Human herpes virus 8 antibodies in HIV-positive patients in Surabaya, Indonesia

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Abstract

Background: Human herpesvirus 8 (HHV-8) infection is etiologically related to Kaposi's sarcoma. Antibodies directed against HHV-8 can be detected in 80-95% of HIV-seropositive patients with KS. HHV-8 serological tests have been done in several countries in Southeast Asia such as Malaysia, and Thailand however no serological data is available in Indonesia. This study was to examine the presence of HHV-8 antibodies in HIV-positive patients in Surabaya, Indonesia.

Material and methods: Ninety-one serum samples were collected from HIV-positive patients in Surabaya, Indonesia. Human immunodeficiency virus-positive serum samples were collected from 10 homosexual men, 25 intravenous drug users (IVDUs) and 56 heterosexuals. Serums were then tested for the presence of HHV-8 antibody by using sandwich ELISA (Abbexa Ltd, Cambridge, UK).

Results: The total of 91 HIV-infected were testing with antibodies to HHV-8 using enzyme-linked immunosorbent assay. Antibodies of HHV-8 were detected in 7/91 (7.7%) of the samples. According to a gender, six men (85.7%) and a women (14.3%) were positive of HHV-8 antibodies. No correlation regarding the gender and age from this study. The antibodies of HHV-8 was detected among intravenous drug users (IVDUs) men 5/7 (42.8%) and 2/7 (28.6%) from homosexual and heterosexual, respectively.

Conclusion: This study found the presence of HHV-8 antibodies in 7.7% of patients in Surabaya, Indonesia. This finding was higher more than Southeast Asian countries. The patients with a positive result could suggest measures to prevent HHV-8 infection.

Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV) is a double-stranded DNA herpesvirus belonging to the γ-herpesvirinae subfamily. Human herpesvirus 8 (HHV-8) or Kaposi's sarcoma–associated herpesvirus (KSHV) is the etiologic agent of Kaposi sarcoma (KS).[1] Kaposi's sarcoma is a tumor developed from cells on lymph nodes or in blood vessels, and can also develop in other parts of the body.[1] Previous studies have shown that immunosuppression is associated with an increased risk of developing KS. Kaposi's sarcoma not only occurs during HIV-1 infection (AIDS-KS), but also in transplant recipients, elderly men of Mediterranean and Middle Eastern origin (classic KS) or in children and adult men from eastern and Central Africa (endemic KS). Kaposi's sarcoma, a tumor most notably associated with the human immunodeficiency virus (HIV) epidemic, occurs in excess among apparently healthy individuals in certain well-defined geographical regions.[2] HHV-8 prevalence exhibits considerable variation in different geographic regions and populations.

The several features suggest that Kaposi Sarcoma unlike other cancers, it may not result from a transformation event that results in autonomously growing tumor cells, but represents the combined effects of a virus with angiogenic properties and local or systemic inflammation.[3]

HHV-8 or KSHV, the only known human herpesvirus (rhadinovirus), is the most recently discovered tumor virus.[4] The genome of KSHV is a linear and the length about 165 to 170 kb.[5] This virus is covered by a tegument containing protein, and closed during budding of the cell. These membranes originate from the outer envelope of the lipid membrane from various specific viral hosts and glycoproteins.[6] It may also exist in a circular episomal form during latency.[7] HHV-8 is most closely related to the gamma-herpesvirus EBV. The HHV-8 genome is an icosahedral capsid of approximately 1,200 angstroms in diameter.[8]

Kaposi's sarcoma is more prevalent in immunosuppressed patients than healthy people. It often occurs in Jewish, Mediterranean, African, and Middle Eastern origins. Seroepidemiological evidence of HHV-8 infection can be used to reflect the epidemiology of Kaposi's sarcoma.[9] Previous study, seropositive prevalence of HHV-8 infection in general population of USA, Northern Europe, and Asia was only around zero to five percent; this was also the case in a seroepidemiological study in Malaysia, Hong Kong, and Sri Lanka where the seroprevalence of HHV-8 was found to be around 3,7%.[10] In East Java, Indonesia, there are detected of HHV-8 antigen about 14.5% [11], but the data about seroepidemiological of HHV-8 antibodies not available. The aim of this study was to explore this omission with an examination of the presence of HHV-8 antibodies in HIV-positive patients in Surabaya, Indonesia.

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Materials and Methods

This study was conducted and approved the Ethics Committee by Universitas Airlangga Hospital. A total of 91 serum samples (53 males and 38 females) were

collected between September and October 2016 from HIV-positive patients in Universitas Airlangga Hospital, Surabaya, Indonesia. The naïve or treated with antiretroviral patients were included, adult HIV-infected (in this case 18-64 years old, and the mean age is 37 years old). There are 6 patient naïve with ARV and 85 with antiretroviral therapy. Informed consent forms were obtained from each of the subjects and personal identifiers were removed to ensure patient confidentiality. A questionnaire regarding age, gender, the possibility route of transmission information was collected. Serum samples obtained were centrifuged and stored at 80˚C until tested. Serum samples were tested to an HHV-8 antibodies by an ELISA method (Abbexa, Cambridge, UK), according to manufacturer instructions.

Results

A total of 91 HIV-infected patients were involved in this study. The majority (93.4%) of the patients had been treated with highly active antiretroviral therapy. The serums samples were tested from 53 males and 38 females, with a mean age of 37 years (range 18–64 years). This study showed that HHV-8 antibodies found in 7 of 91 samples (7.7%). Six men (85.7%) and a women (14.3%) were positive of HHV-8 antibodies. No correlation among different age group. Two of seven positive with antibodies of HHV-8 was naïve patient and five patient were used antiretroviral therapy. HHV-8 antibodies were detected in 3/7 (42.8%) among intravenous drug users (IVDUs) men and 2/7 (28.6%) was detected from homosexual and heterosexual orientation, respectively. The determinations of HHV-8 in HIV-positive is shown in Table 1.

Discussion

Epidemiological studies of HHV-8 infection depend on serological tests because viremia is detected in some infected people without symptoms.[12,13] As a result of research conducted in Surabaya, Indonesia is an interesting comparison with other studies around the world. This research refers to a previous study that hhv 8 antigen was detected, but the case of Kaposi's Sarcoma is very rare. Serological detection of hhv-8 in this study yielded lower results than antigens detected in the same case, HIV- positive patients. Previous studies, the presence of HHV-8 antigen was detected in 14.56% of HIV-positive patients in East Java, Indonesia.[11] Antibodies of HHV-8 was detected 7.7% in Surabaya. This result was lower compared to other studies, e.g., Thailand was detected 28%,[14] Xinjiang, China 31.2%,[15] Nigeria 62%[16] and Cameroon 70%,[17] India 26.6%.[18]

This result of study, 42.8% HIV-infected intravenous drug users were positive HHV-8 antibodies. Heterosexual and homosexual men were detected 28.6%, respectively. Ayuthaya and colleagues' research reports that in Thailand, the presence of HHV-8 lytic antigen in 12% HIV-positive homosexual men, 16% heterosexual men, and 9% IVDUs.[19] In Western countries, KSHV seroprevalence rates ranged around 20% to 40% among homosexual men, but were very low, usually below 5% to 10%, in HIV-infected intravenous drug users, women, and patients with hemophilia. Given that the rate of AIDS KS among HIV-infected homosexual men in Western countries in the 1980s was in a similar range, these initial cross-sectional studies suggested that most KSHV in HIV-infected homosexual men would eventually develop into KS.[20,21] HHV-8 without KS in serum samples are detected 4% and AIDS-KS are 42.8% in Brazil[22] and Germany are detected 52% and AIDS-KS are 91%.[23] In HIV-positive patients without Kaposi Sarcoma, 4% were positive using PCR method. These patients certainly present a higher risk of developing AIDS-KS.[20] In previous study, the progression of KSHV infected to KS was faster after HIV infection.[20] This may be the result of primary KSHV infection in an already immunocompromised individual being more extensive and severe than in an immunocompetent person. The rapid development to KS within a few weeks after KSHV seroconversion in immunocompromised patients as a result of HIV infection or transplantation.[20,21]

The presence of HHV-8 infection in HIV-positive patients is possibly related to the risk of developing opportunistic diseases, including Kaposi's sarcoma (classic, AIDS-related KS, endemic and iatrogenic) and other proliferative diseases, such as primary effusion lymphoma and multicentric Castleman disease. Among immuno-competent people, only a small proportion of HHV-8 infections develop into Kaposi sarcoma. The mechanism of HHV-8 to develop into KSHV has many considerations. Some studies mention that KSHV can promote the proliferation of primary endothelial cells. Infection of endothelial cells leads to their transformation and proliferation. Invasion of the subendothelial cell layer, such as the dermis of the skin, occurs. Proliferation is mainly driven by cytokine stimulation of latently infected cells in a paracrine manner. Viral cytokines such as vIL-6, a homologue molecule of human IL-6, stimulates the production of VEGF. Viral IL-6, produced by latent and lytically infected cells, is able to stimulate the gp130 chain of the IL-6 receptor and results in modulation of gene transcription. The viral GPCR, a constitutively active homologue of the IL-8 receptor, is expressed in lytically infected cells and also alters intracellular signaling pathways to promote cell transformation and cytokine production. The secretion of VEGF is a primary driver of endothelial cell proliferation via the VEGF receptor. Most of the proliferating cells are latently infected with HHV-8 and develop into characteristic spindle cells.[24]

Various tests have detected HHV-8 antibodies in the majority of asymptomatic individuals with increased tumor risk, including HIV-positive homosexual men,[25]

Table 1. Determinants of HHV-8 antibodies in HIV-infected patients

Characteristic	N	HHV-8 positive N (%)	P value
Age group (years)			
A: ≤ 30	23	3 (13.04)	
B: 31-40	39	2 (5.1)	p: 0.6 (NS)
C: >40	29	2 (6.9)	
Sex			
Male	53	6 (11,3)	p: 0.1 (NS)
Female	38	1 (2.6)	
Sexual orientation			
Homo/bisexual	10	2 (20)	
Heterosexual	81	5 (6.17)	
Possibility route of HIV infection			
Sex transmission	61	4 (6.5)	
Sharing needles or syringes	25	3 (12)	
Vertical route (mother to child)	-	-	
Unknown	5	-	

p<0,05, S (Significant), NS (Not Significant).

adults from Italy and various regions of sub-Saharan Africa[26, 27] and some low risk people, such as blood donors from the UK, USA, and Jamaica.[28,29] Several studies using different serological tests found that almost 100% patients with different clinical forms of Kaposi's sarcoma had a high titer of the HHV-8 antibody, which had been detected before the appearance of clinical lesions of Kaposi's sarcoma.[13,30,31] Current evidence suggests that HHV-8 infection is a prerequisite in the pathogenesis of Kaposi's sarcoma, but factors relating to the host immunodeficiency may greatly increase the incidence of Kaposi's sarcoma among subjects infected with HHV-8.

Antiretroviral also may have a role in the treatment of HHV-8-related disease independent of its immune-restorative properties in persons with HIV. In addition to the previously mentioned effects on HHV-8 shedding and viremia, zidovudine and stavudine both have been shown to be competitive inhibitors of the HHV-8 thymidine kinase,[32,33] and ritonavir demonstrates a strong antitumorigenic effect against KS.[34,35]

Conclusions

The presence of HHV-8 antibodies was found in 7.7% of the HIV-positive patients who participated in this study. Based on these results found in patients among Surabaya, further examination should be conducted on patients living with HIV. This would assist with early detection and subsequent management of any clinical manifestations related to HHV-8 infection, especially in the form of Kaposi's sarcoma lesion. The patients with a positive result could suggest measures to prevent HHV-8 infection.

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