

HUMAN HERPESVIRUS-6 MENINGOENCEPHALITIS AND PULMONARY TUBERCULOSIS IN HIV PATIENT: A CASE REPORT

Meningoensefalitis Human Herpesvirus-6 dan Tuberkulosis Paru pada Pasien HIV: Laporan Kasus

Hanindia Riani Prabaningtyas, Stefanus Erdana Putra, Muhammad Hafizhan, Diah Kurnia Mirawati, Pepi Budianto

AFFILITIONS

Neurology Department,
Faculty of Medicine,
Universitas Sebelas Maret,
Surakarta, Indonesia

ABSTRACT

Human herpesvirus 6 (HHV-6), the causative agent of exanthema subitum in childhood, could also induce meningoencephalitis in immunocompromised individuals. We reported a case of 32-years-old woman with complaints of worsen headache, one week before admission. She also had intermittent fever and weakness in her left limb. She was admitted to a local hospital, suspected with tuberculous meningitis and pulmonary tuberculosis, and treated with anti-tuberculosis drugs, antibiotics for bacterial meningitis and steroids. She did not show any improvement, and then referred to X Surakarta General Hospital. On physical examination, we found GCS of E3V3M5, crackles and wheezing throughout the lung, neck stiffness, left hemiparesis, and clonus of the left lower leg. Laboratory results showed increasing leukocytes, reactive anti-HIV, and positive PCR for HHV-6 in the cerebrospinal fluid. On the CT scan, there were multiple hypodense lesions in the pons and right internal capsule, and communicant hydrocephalus. She was treated with highly active anti-retroviral therapy (HAART), Valganciclovir 900 mg b.i.d., steroid, anti-tuberculosis drugs and symptomatic treatment. After three weeks of admission, she began to show improvement, level of consciousness increased, and allowed went home.

KEYWORDS:

HHV-6, Meningoencephalitis, HIV, Valganciclovir

ABSTRAK

Human herpesvirus-6 (HHV-6), agen penyebab eksantema subitum pada masa kanak-kanak, juga dapat menyebabkan meningoensefalitis pada individu dengan gangguan sistem imun. Kami melaporkan sebuah kasus, seorang wanita berusia 32 tahun dengan keluhan nyeri kepala yang semakin memberat sejak satu minggu sebelum masuk rumah sakit. Selain itu, pasien juga mengeluh demam intermiten dan kelemahan pada tungkai kiri. Pasien dirawat di rumah sakit lokal dengan diagnosis suspek meningitis tuberkulosis dan tuberkulosis paru dan ditatalaksana dengan obat anti tuberkulosis, antibiotik untuk meningitis bakteri dan steroid. Karena tidak ada perbaikan, pasien dirujuk ke RS X Surakarta. Pada pemeriksaan fisik ditemukan GCS E3V3M5, ronki dan mengi di seluruh lapang paru, kaku kuduk, hemiparesis kiri, dan klonus tungkai bawah kiri. Hasil laboratorium menunjukkan peningkatan leukosit, anti-HIV reaktif, dan PCR HHV-6 positif pada cairan serebrospinal. Pada CT-scan ditemukan lesi hipodens multipel pada pons dan capsula interna kanan serta hidrosefalus komunikan. Pasien ditatalaksana dengan highly active anti-retroviral therapy (HAART), Valgansiklovir 900mg/12 jam, steroid, obat anti tuberkulosis dan pengobatan simptomatik. Setelah perawatan selama tiga minggu, pasien mulai menunjukkan perbaikan, tingkat kesadaran meningkat, dan diperbolehkan pulang.

KATA KUNCI:

HHV-6, Meningoensefalitis, HIV, Valgansiklovir

CORRESPONDING AUTHOR:

Hanindia Riani Prabaningtyas
hanindiarp.12@staff.uns.ac.id

INTRODUCTION

Human herpesvirus type 6 (HHV-6) is a member of the Herpesviridae family that is commonly recognized as the cause of roseola infantum – a mild and self-limiting viral syndrome

that occurs during childhood (Clark, 2016). The lymphotropic HHV-6 was first isolated in 1986 in patients with lymphoproliferative disorders or human immunodeficiency virus (HIV) infection, and was further classified into two subtypes (variants A



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

and B) in 1993, when key epidemiological and molecular differences were identified (Clark, 2016; Balakrishna et al., 2018). In some cases, primary infection leads to exanthema subitum, which is rarely complicated by meningoencephalitis. After primary infection, HHV-6 is characterized by life-long latency in peripheral blood mononuclear cells (PBMCs), salivary glands, and brain tissue (Bozzola et al., 2012). Reactivation of infection occurs occasionally, causing fever, rash, pneumonitis, hepatitis, and, in some cases, encephalitis, during pharmacological immunosuppression or acquired immunodeficiency (Reynaud and Horvat, 2013). In immunocompetent adults, this herpesvirus is related to a mononucleosis-like syndrome, Sjogren syndrome, Hodgkin and non-Hodgkin lymphomas and meningoencephalitis (Munawwar and Singh, 2016). Recently, HHV-6 has been associated as an emerging pathogen in patients with acquired immune deficiency syndrome (AIDS) and recipients of bone marrow and solid organ transplants. Meningoencephalitis that occurs in patient with immunosuppression is the most serious clinical manifestation associated with HHV-6 infection or reactivation (Munawwar and Singh, 2016).

Here, we describe 32-years-old woman with encephalitis related to reactivation of HHV-6. In contrast to patients described elsewhere, our patient was confirmed with pulmonary tuberculosis, and HIV. The initial symptoms of this case were

chronic headache, decreased level of consciousness, left hemiparesis, and Oculomotor nerve palsy.

CASE REPORT

A 32-years-old woman was referred from a private hospital, suspected with meningoencephalitis. Anamnesis revealed that she had throbbing headache one week prior to admission. Her headache was relieved after taking over the counter medication, but it relapsed few hours later. She also had fever, but did not have any nausea, vomitus, glare, blurred vision, seizures, or weakness. She was brought to the hospital by her family and was admitted to isolation ward due to pulmonary tuberculosis. No improvement was observed after treatment and she began to notice that she had weakness on her right limb. She began to be unresponsive and was referred to Dr. Moewardi General Hospital. A year before admission, she had unintentional weight loss. She also had persistent cough with phlegm, without blood and frequent night sweats. She did not seek any treatment for those symptoms. Her family often found her having a mood-swing and refused to eat after a miscarriage four months prior to admission. She had no history of vaccination. There was no family history of similar symptoms. There is no history of overseas travel before admission.

On physical examination, she was sub-febrile, normotensive, and bradycardic, with a heart

rate of 52 times/min and a respiratory rate of 18 times/min. She was disoriented to person, place, and time, her pupils were round, regular, isochoric, and reactive to light. We also found neck stiffness, positive Brudzinski I sign, bilateral papilledema, paresis of right Oculomotor nerve, and left hemiparesis.

Diagnostic lumbar puncture (LP) revealed colorless, clear, cerebrospinal fluid (CSF) with no clot. We also discovered positive Nonne-Pandy's test, total protein of 70 mg/dl, glucose level of 45 mg/dL, total cell of 45 cells/ μ L, with 0% polymorphonuclear (PMN), and 100% mononuclear (MN) cell. We also found random blood sugar (RBS) level of 92 mg/dL.

Her chest X-ray showed that active, broad lesion of pulmonary tuberculosis (TB) with mixed pneumonia, multiple bullae in the left supra hiller, and left pleural effusion. Brain CT-scan showed multiple hypodense lesions in the pons and right internal capsule constituting an inflammation process, communicant hydrocephalus, and cerebral edema.



Figure 1. Chest X-ray showed active pulmonary tuberculosis.

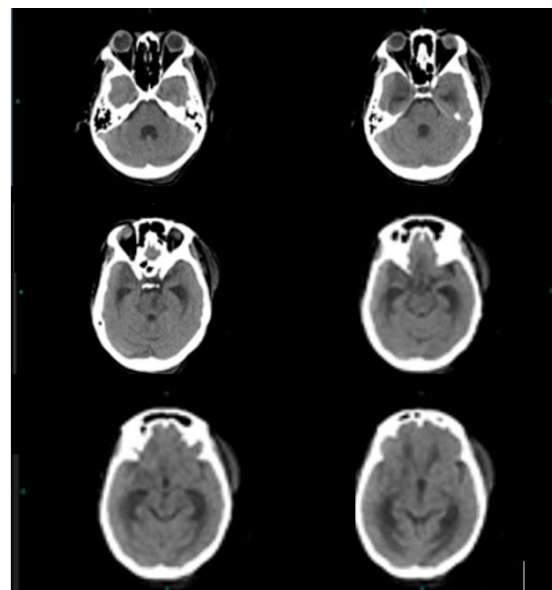


Figure 2. Brain CT scan showed multiple hypodense lesions in pons and right internal capsule.

In the emergency department, prophylactic Dexamethasone 10mg q.i.d. and Acetazolamide 500mg was given to reduce intracranial pressure.

Meningitis/encephalitis nucleic acid amplification testing (NAAT) of CSF sample using nested PCR was done after performing LP in the ward. Five microliters of extracted DNA from CSF sample were amplified in a 50 μ l reaction mixture

containing PCR buffer (10 mM Tris-HCl, pH 8.3; 50 mM KCl, and 1.5 mM MgCl₂), 200 μM each dNTP, 1-unit Taq polymerase (Pharmacia Biotech) and 0.25 μM of each primer. HHV-6 DNA was detected in the CSF, thus Valganciclovir 900mg b.i.d. was administered. Both Acetazolamide and Valganciclovir were continued to relief increasing intracranial pressure symptoms. Oral anti tuberculosis therapy was prescribed by Department of Pulmonology.

Anti-HIV test resulted positive, with CD₄⁺ lymphocyte count of 52 cell/mm³, and highly active antiretroviral therapy (HAART) was administered following the recommendation that HAART should be given as soon as the patient is clinically stable on anti-TB therapy and not later than 12 weeks after starting anti-TB therapy (Munawwar and Singh, 2016).

After 10 days of care, her level of consciousness was improved, but she still complained about left extremity weakness and double vision. She was discharged on the 21st day with improved symptoms. She was prescribed with Acetazolamide and Valganciclovir 900 mg b.i.d. There were no complaints of hearing loss or balance disturbance after receiving treatment.

DISCUSSION

Case of HHV-6 induced meningoencephalitis in HIV patients is rare, with only few cases were reported on medical literature. The role of HHV-6 in

the pathogenesis of central nervous system (CNS) disease remains unclear (Munawwar and Singh, 2016). Several literatures found that HHV-6A and HHV-6B are ubiquitous viruses that are detected in all human populations around the world (Bozzola et al., 2012; Munawwar and Singh, 2016). The role of HHV-6 as pathogen in this CNS disease was discovered after the detection of HHV-6 DNA in the CSF. HHV-6 was the only pathogen isolated from the patient's CSF at the time of acute neurological illness. HIV and HHV-6 may have a synergistic activity; both viruses infect and replicate in T CD₄⁺ lymphocytes. Furthermore, HIV may enhance the replication and dissemination of HHV-6. The role of HHV-6 on CNS infection in immunocompromised patient is difficult to understand since HHV-6 is frequently identified with other opportunistic pathogens. In this case, our patient had pulmonary tuberculosis, which leads to a misdiagnosis. HHV-6 may be considered an emergent pathogen in AIDS patients that can act directly or indirectly, and could interfere different components of the immune system (Reynaud and Horvat, 2013; Tesini *et al.*, 2014).

Magnetic resonance imaging (MRI) on HHV-6 infection generally reveals the meningeal contrast-enhancement signal intensity abnormality in the medial temporal lobe and hyperintense lesions in the insula, amygdala and the inferior frontal lobe, which appear similar to MRI of type-1 herpes

simplex virus (HSV) infection. Some patients can present with periventricular lesions hypointense in T1 and hyperintense in T2, indicating vascular damage (Corti *et al.*, 2007). However, MRI brain findings might be completely normal in some cases, particularly in immunocompromised patients. In this case, our patient had only a plain head CT-scan, since the nested PCR examination already revealed the definite diagnosis.

The general strategy of antiviral therapy for HHV-6 infection may be based upon the current treatment of anti-human cytomegalovirus (anti-HCMV). The essential target is active infection. But, available drugs on the market are not efficient against active infection, thus treatments are limited to prophylactic and pre-emptive approaches (Shahani, 2014).

However, one must keep in mind that many active HHV-6 infections are asymptomatic, even in individual with immune deficiency, and can revert to latency without any therapy. Moreover, if an active HHV-6 infection is suspected, it is essential to rule out the possibility of HHV-6 reactivation (Shahani, 2014). If the latter is true, then virus reactivation may still have occurred and may be a potential source of disease. However, the patterns of transcription, indicating active virus replication are not completely known, and the quantification of transcripts is not yet standardized, which makes

the interpretation of virologic findings ambiguous in many cases (Shahani, 2014).

Clinical presentation of HHV-6 encephalitis includes headache, memory impairment, confusion, seizures, altered mental status and focal neurological deficits (Bozzola *et al.*, 2012). Our patient presented with headache, decreased level of consciousness, left extremity weakness and diplopia.

Opportunistic infections can cause a variety of ocular disorders in patient with HIV. Retrobulbar optic neuritis is rare and may be caused by herpesviruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella-zoster virus (VZV) (Jabs, 1995) and HHV-7 (Yoshikawa *et al.*, 2003), while syphilis and cryptococcus are the most important non-viral etiologies. In our case, microbiological examination of CSF samples only identified HHV-6. HIV could have been involved as a primary pathogen in optic neuritis or Oculomotor nerve palsy, but the moderate HIV viral load in the CSF contrasting with the high level in plasma, and the low ratio CSF/plasma, adding to the visual complaint before HAART introduction were strong arguments for the solely pathogenic role of HHV-6 infection. On the other side, retrobulbar optic neuritis and Oculomotor nerve palsy might also be worsen as an adverse effect of antiretroviral drugs, particularly Didanosine and Zidovudine (Cobo *et al.*, 1996).

Three drugs initially developed to target HCMV infection have been shown to be efficient against HHV-6 infection, both in vitro and in vivo: Ganciclovir, Foscarnet, and Cidofovir (Agut *et al.*, 2015). Acyclovir, a widely available antiviral drug against HSV and VZV infections, is active against HHV-6 in vitro, but only at very high concentrations. The three efficient anti-HHV-6 compounds exhibit the same inhibition activity against both HHV-6A and HHV-6B in vitro (Bozzola *et al.*, 2012; Agut *et al.* 2015). The mechanisms of this antiviral activity are similar for both HCMV and HHV-6: the viral DNA polymerase is specifically inhibited by the tri-phosphorylated form of Ganciclovir, and the di-phosphorylated form of both Cidofovir, and Foscarnet (Yamanishi *et al.*, 2013; Agut *et al.*, 2015). Ganciclovir and Foscarnet have been known to be effective against HHV-6 and previous case reports have demonstrated good clinical outcomes with both drugs. In this case, our patient was treated with Valganciclovir for 21 days, due to unavailability of Ganciclovir, Cidofovir, and Foscarnet.

CONCLUSION

Central nervous system (CNS) involvement due to HHV-6 should be considered in meningoencephalitis case with advanced HIV/AIDS and T CD₄⁺ cell counts less than 200 cells/ μ L. Abnormal CSF analysis may help to diagnose encephalitis caused by HHV-6, as it was in our

case. The diagnosis is confirmed by the detection of HHV-6 genome by PCR. Early diagnosis followed by specific therapy based on Ganciclovir or Foscarnet and HAART could improve patient's condition.

ACKNOWLEDGEMENT

The author would like to thank Director of Dr. Moewardi General Hospital for the permission to publish this case.

REFERENCES

- Agut, H., Bonnafous, P., and Gautheret-Dejean, A. 2015. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev.* 28(2). Pp: 313–35. doi: 10.1128/CMR.00122-14
- Balakrishna, J.P., Bhavsar, T., Nicolae, A., Raffeld, M., Jaffe, E.S., and Pittaluga, S. 2018. Human Herpes Virus 6 (HHV-6) Associated lymphadenitis – Pitfalls in Diagnosis in Benign and Malignant Settings. *Am J Surg Pathol.* 42(10). Pp: 1402–8.
- Bozzola, E., Krzysztofciak, A., Bozzola, M., Calcaterra, V., Quondamcarlo, A., Lancellata, L., and Villani, A. 2012. HHV6 meningoencephalitis sequelae in previously healthy children. *Infection*, 40(5). Pp: 563–6. doi: 10.1007/s15010-012-0295-9.
- Clark, D.A. 2016. Clinical and laboratory features of human herpesvirus 6 chromosomal integration. *Clin Microbiol Infect.* 22(4). Pp: 333–9. doi: 10.1016/j.cmi.2015.12.022.
- Cobo, J., Ruiz, M.F., Figueroa, M.S., Antela, A., Quereda, C., and Perez-Elias, M.J. 1996. Retinal toxicity associated with didanosine in HIV-infected adults. *AIDS.* 10. Pp: 1297–300.
- Corti, M.E., Villafañe, O.J., and Palmieri. 2007. Viral Opportunistic Infections. *Atlas of Neuroimages and Neuropathology of HIV/AIDS Disease.* 1st edn. Buenos Aires. Pp: 29–35.
- Jabs, D.A. 1995. Ocular manifestations of HIV infection. *Trans Am Ophthalmol Soc* 93. Pp: 623–83.

- Munawwar, A. and Singh, S. 2016. Human Herpesviruses as Copathogens of HIV Infection, Their Role in HIV Transmission, and Disease Progression. *J Lab Physicians*. 8(01). Pp: 005–18. doi: 10.4103/0974-2727.176228.
- Reynaud, J.M. and Horvat, B. 2013. Human Herpesvirus 6 and Neuroinflammation. *Virology*. 1. doi: 10.3109/10428199409049719.
- Shahani, L. 2014. HHV-6 encephalitis presenting as status epilepticus in an immunocompetent patient. *BMJ Case Rep*. Pp: 1–3. doi: 10.1136/bcr-2014-205880.
- Tesini, B.L., Epstein, L.G., and Caserta, M.T. 2014. Clinical impact of primary infection with roseoloviruses. *Curr Opin Virol*. 9. Pp: 91–6. doi: 10.1016/j.coviro.2014.09.013.
- Yamanishi, K., Mori, Y., and Pellett, P.E. 2013. Human Herpesviruses 6 and 7. *Fields Virology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins. Pp: 2058–79.
- Yoshikawa, T., Yoshida, J., Hamaguchi, M., Kubota, T., Akimoto, S., Ihira, M., Nishiyama, Y., and Asano, Y. 2003. Human herpesvirus 7-associated meningitis and optic neuritis in a patient after allogeneic stem cell transplantation. *J Med Virol* 70. Pp: 440–3.