Concomitant Herpes Simplex Virus Type 1 and Cytomegalovirus Encephalitis in an AIDS Patient

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ABSTRACT

Cytomegalovirus (CMV) infection of the central nervous system (CNS) is frequently observed in patients with AIDS. In contrast, CNS infection with herpes simplex virus type 1 or 2 (HSV-1 or HSV-2) is uncommon in AIDS patients. In addition, CMV and HSV co-infection is rarely described. We reported a case of 40-year-old HIV-infected woman who presented with dull aching headache for two months and three days of high grade fever with alteration of consciousness. Magnetic resonance imaging of the brain showed multiple areas of encephalitis in the medulla oblongata, cerebellum, bilateral medial temporal lobes and left insular region. Ependymitis was suspected. Polymerase chain reaction (PCR) of cerebrospinal fluid was positive for both herpes simplex virus type 1 and cytomegalovirus. (J Infect Dis Antimicrob Agents 2011;28:105-10.)

Note: This case had been presented and discussed in the Interhospital Case Conference on Infectious Diseases (ICCID), 23 December 2010, Bangkok, Thailand.

INTRODUCTION

Cytomegalovirus (CMV) infection of the central nervous system (CNS) is frequently observed in patients with AIDS.1 It occurs in patients with advanced immunocompromised state i.e. CD4 cell counts <50 cells/mm³. It is often concomitant with CMV infection of other organs, including retinitis, adrenalitis, and pneumonitis.2 In contrast, CNS infection with herpes simplex virus (HSV) type 1 or 2 is uncommon in AIDS patients and often clinically and pathologically atypical.3

In this report, we illustrate a 40-year-old HIV-infected woman with possible CMV and HSV type-1 co-infection of the central nervous system.

CASE REPORT

A 40-year-old refugee woman from Chiang Mai...
had been diagnosed as HIV infection since October 2009, when she had disseminated *Penicilliosis marneffei* and bilateral CMV retinitis. She completed treatment with amphotericin B followed by itraconazole orally for disseminated *Penicilliosis marneffei* and intravitreal ganciclovir injection for CMV retinitis. She received neither combined antiretroviral therapy (cART) nor medications for opportunistic infection (OI) prophylaxis due to economic problem. She was admitted to the hospital on October 13, 2010 with a history of high grade fever and alteration of consciousness for 3 days. She had dull aching headache around occipital area for two months and horizontal diplopia for two weeks.

Physical examination revealed her vital signs as follows: body temperature 38.5°C, respiratory rate 18/min, pulse rate of 88/min, and blood pressure 100/70 mmHg. She was drowsy. Neurological examination revealed bilateral 6th nerve palsy. Ophthalmologic finding revealed exudate and hemorrhage in both eyes, which were the same as the last follow-up visit after CMV retinitis therapy. Pupillary reactions were normal. There was no stiffness of neck.

Complete blood count revealed a hematocrit of 25.8%, total white blood cell count 2.3 x 10^9/L (neutrophil 85.3%, lymphocyte 5.2%, monocyte 6.6%, basophil 0.3%, eosinophil 2.6%), and platelet count of 118 x 10^9/L. Blood chemistry results were as follows: sodium 124, potassium 3.1, chloride 93, and bicarbonate 16 mmol/L. Other blood chemistries were within normal range. Chest X-rays were normal. Her CD4 cell count was 3 cells/mm^3 (2%).

A cranial computed tomography (CT) on the first day of admission revealed open pressure 9.5 cmH2O and white blood cell count of 62 cells/μL (mononuclear cells 96% and polymorphonuclear cells 4%). Cerebrospinal fluid (CSF) protein and glucose were 160 and 48 mg/dL, respectively. CSF cryptococcal antigen titer was negative. She was initially treated with ceftriaxone 2 g intravenously every 12 hours on the 6th day of admission. However, she still had high grade fever and her consciousness was deteriorated. Magnetic Resonance Imaging (MRI) brain was subsequently performed on the 8th day of admission and revealed multiple areas of encephalitis in the medulla oblongata, cerebellum, bilateral medial temporal lobes, left insular region and the posterior limb of the internal capsule as shown in Figure 2. Ependymitis was suspected. She was finally intubated on the 9th day of admission and intravenous ganciclovir 250 mg every 12 hours was started. On the 14th day of admission, she developed coma. A cranial CT was then performed and revealed intracerebral hemorrhage along cerebellar folia, cerebellar vermis and medial aspect of left temporal lobe. Intraventricular hemorrhage was shown in 3rd ventricle, 4th ventricle, and foramen of Lushka. Tonsillar and bilateral ascending transtentorial herniation was noted. Neurosurgery was consulted for ventriculostomy but her relatives denied further treatment and brought her home. Qualitative polymerase chain reaction (PCR) for herpes simplex virus type 1 and cytomegalovirus were both positive. CSF PCR for herpes simplex virus type 2 and mycobacterial tuberculosis were negative.

**DISCUSSION**

HSV type 1 encephalitis is a relatively uncommon disease that usually occurs in otherwise healthy individuals. HSV encephalitis, if left untreated, resulted in mortality of greater than 70% and survivors usually
Figure 1. CT brain on the first day of admission revealed only old lacuna infarction at bilateral internal capsule with normal ventricle and brain parenchyma. No abnormal enhancement was seen after intravenous contrast injection.

Figure 2. MRI 7 days later demonstrates multiple hyperintense lesions on T2 and flair technique at bilateral temporal, occipital, cerebellum, and medullar oblongata. Increase signal intensity of ependymal lining of lateral ventricle on all flair, T2 weighted image (T2WI), and diffuse weighted image (DWI) (figure shows only flair image). No abnormal enhancement lesions were seen.
have severe neurologic sequelae.\textsuperscript{4} Chretien F et al.
reported 11 cases of herpes simplex encephalomyelitis in AIDS patients. Three of them presented with a
typical, necrotizing, limbic encephalitis. Other clinicopathological patterns included ventriculitis,
rhombencephalitis and myelitis. Ventriculitis and rhombencephalitis were usually caused by HSV-1,
whereas myelitis was mostly caused by HSV-2 infection. Co-infection with cytomegalovirus was found
in 9 of these cases.\textsuperscript{3}

Encephalitis caused by CMV in patients without acquired immunodeficiency syndrome (AIDS) is relatively rare. It usually occurs only in immunosuppressed patients.\textsuperscript{5} Disseminated CMV infection and/or encephalitis has been recognized as a frequent cause of opportunistic infections in
patients with AIDS.\textsuperscript{2} Patients with CMV encephalitis show similar features to those with AIDS dementia
but tend to have a more acute onset and more prominent confusion/disorientation or apathy/withdrawal. Hyponatremia and cranial nerve involvement were also noted more frequent in CMV encephalitis.\textsuperscript{6}

Combined CMV and HSV encephalitis has also been described in three patients by Laskin OL et al. All three cases had a diffuse ventriculoencephalitis documented at postmortem examination. The presence of HSV-1 and CMV was confirmed microscopically with immunohistochemistry. None of these cases were
diagnosed as HSV encephalitis ante mortem. These three cases had been seen at a single institution over approximately one year, thus it seems to indicate that CMV and HSV co-infections of the CNS are not rare in patients with AIDS.\textsuperscript{7}

Eighty-two autopsy cases with a histological diagnosis of CMV necrotizing encephalitis were examined retrospectively.\textsuperscript{8} Concomitant CMV/HSV infections were demonstrated by immunohistochemistry
in 13 cases (16%). HSV-1 was found in 9 cases and HSV-2 in 4 cases. Co-infection of the CNS with CMV
and HSV of either type 1 or type 2 was demonstrated in a significant proportion of AIDS patients with necrotizing encephalitis.\textsuperscript{8}

HSV-PCR of the CSF is the diagnostic method of choice for herpes simplex encephalitis.\textsuperscript{9} PCR has a
high sensitivity, specificity, positive predictive value, and negative predictive value.\textsuperscript{9} However, neither sensitivity nor specificity of the test is 100 percent. HSV-PCR of the CSF should be interpreted cautiously within the context of the clinical manifestation of the patient. CSF PCR for the detection of CMV DNA is the most sensitive diagnostic method for CMV infections of the CNS. Its diagnostic reliability has been widely evaluated in AIDS patients. In most of the studies, both the sensitivity and the specificity were higher than 80%, and the positive predictive values and negative predictive values varied between 86–92% and 95–98%, respectively.\textsuperscript{9} Specificity of CSF PCR remained high even when control patients with extracerebral CMV disease were included.\textsuperscript{10} The detection of CMV DNA in the CSF is strongly predictive of the presence of CMV lesions in the CNS and is generally associated with clinical encephalitis. Therefore, a positive PCR result requires a careful interpretation in the individual clinical context. In addition, CMV DNA-positive samples could be further analyzed by quantitative PCR for better interpreting CSF PCR results. Quantitative PCR could be useful in evaluating the extent of involvement\textsuperscript{11} and monitoring antiviral therapy.\textsuperscript{12}

This case report supports the evidence of concomitant HSV-1 and CMV encephalitis in AIDS patients. Therefore, in a patient with a history of CMV disease and presented with clinical findings of viral encephalitis, the possibility of concomitant HSV and CMV infection should not be excluded. Unfortunately, quantitative PCR for CMV DNA was not performed
in this case. This patient was diagnosed as CMV retinitis 1 year prior; therefore, might have low level of CMV DNA in the CSF. However, the evidence of ventriculoencephalitis represents a distinct form of CMV infection of the CNS in terms of neuropathological characteristics.13

In terms of treatment, the drug of first choice for HSV encephalitis is acyclovir. The recommended dose of acyclovir is 10 mg/kg IV q 8 hr with dose adjustment for renal insufficiency. For favorable results, antiviral therapy needs to be initiated as early as possible.14 For CMV encephalitis, the drug of first choice is ganciclovir. The induction phase requires intravenous ganciclovir 5 mg/kg/day every 12 hours for 14 days, followed by the maintenance phase with intravenous ganciclovir 5 mg/kg/day daily indefinitely. Foscarnet, the recommended alternative drug, at a dose of 90 mg/kg intravenously every 12 hours for 14 days in the induction phase is recommended, followed by 90 mg/kg/day in maintenance phase indefinitely.6 Patients who have failed or have become intolerant to these drugs may have benefit from cidofovir 5 mg/kg/day for 2 weeks, followed by 5 mg/kg every 2 weeks.6 This drug is nephrotoxic and should be given with intravenous fluid hydration and high doses of probenecid before and after cidofovir injection.6 For CMV and HSV co-infections, ganciclovir demonstrates in vitro activity against both viruses.15 However, clinic trials support the use of ganciclovir in HSV encephalitis therapy is still lacking.

References


