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Ganciclovir-resistant human herpesvirus-6 encephalitis in a liver transplant patient: a case report

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Abstract Human herpesvirus-6 (HHV-6) was initially isolated in 1986 from patients with lymphoproliferative disorders (Ablashi et al. 1987). Since that time, two genetically distinct variants were sequenced, HHV-6A and HHV-6B (Ablashi and Balachandran 1991). Both variants have been linked with neurologic disease (Crawford et al. 2007). HHV-6 encephalitis has been well described in literature, typically presenting with confusion, coma, seizure, and headache. The majority of HHV-6 encephalitis has been limited to post-transplant recipients (Singh and Paterson 2000). Encephalitis due to HHV-6 infection has been reported in two liver transplant recipients (Massih and Razonable 2009 and Montejo et al. 2002). Although there has been in vitro studies regarding the potential resistance patterns for HHV-6 virus, there has been only one clinic case report supporting these findings (Isegawa et al. 2009). We describe the first case of ganciclovir-resistant HHV-6 encephalitis in a post-liver transplant patient.

Case report

A 71-year-old male with a past medical history significant for liver transplant 2 months prior, presented to the hospital with generalized tonic–clonic seizures. The patient was in good health until his wife found him unresponsive, and subsequently witnessed a generalized tonic–clonic seizure. Upon arrival to the hospital, the patient was intubated secondary to altered mental status, agitation, and inability to protect his airway.

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On neurologic examination, the patient was unable to follow commands after sedation was discontinued. He was unable to track to voice or visual stimuli, requiring constant tactile stimulation to keep eyes open. There was no evidence of meningismus. He displayed intact cough, corneal, and pupillary light reflexes. Extraocular movements were significant for intermittent spontaneous forced left gaze deviation with return to mid position. Oculocephalic maneuver displayed incomplete adduction of left eye. Motor examination was significant for grimacing and brisk withdrawal to painful stimuli in all four extremities. There were no spontaneous movements or abnormal posturing of the extremities. Deep tendon reflexes were symmetric and brisk, with flexor plantar responses.

Other past medical history included esophageal varicies, and liver transplant due to hepatitis C cirrhosis. The patient was maintained on Prograf with a level of 5.8 upon admission. His post-transplant course was complicated by primary cytomegalovirus (CMV) infection for which he was being treated with IV Ganciclovir. The patient was started on IV ganciclovir 400 mg q12 at home. His serum CMV viral load peaked at 415,884 copies/ml. His serum viral load fell to 382 copies/ml 1 week later, and then became negative on weeks 3 and 4 of treatment. The patient remained on IV ganciclovir until admission for his encephalitis.

The patient was found to be neutropenic on admission with an absolute neutrophil count of 0.6. EEG was abnormal due to presence of low-voltage sharp waves originating from the left frontal/anterior temporal head region, intermittent electrographic seizures, and frequent left temporal periodic lateralized epileptiform discharges. MRI brain revealed multifocal T2 hyperintensities most prominent in the left mesial temporal lobe, pons, and cerebellum, as well as bilateral parietal occipital hyper-

intensities (Fig. 1). Lumbar puncture was performed; the opening pressure was 18 mmHg, WBC 0, RBC 0, glucose 78, and protein 97. Cerebral spinal fluid (CSF) culture for bacteria and fungus was negative. Viral PCR on CSF was negative for VZV, EBV, CMV, and HSV 1 & 2. CSF lyme, RPR, and *Cryptococcus* antigen were also negative. CSF was positive for HHV-6 with DNA titer of 1,162 copies/mL. HHV-6 plasma DNA titer was 252,240 copies/mL.

The patient was diagnosed with acute encephalitis involving the temporal, occipital, cerebellar, and brainstem structures. The encephalitis was secondary to ganciclovir-resistant HHV-6 infection. Because the patient acquired this infection while on IV ganciclovir, he was treated aggressively with phosphonoformic acid (foscarnet) 40 mg/kg IV q12 h. His serum viral HHV-6 titers were monitored weekly with successful therapeutic response (Fig. 2). Clinically, electrographically, and radiologically, the patient improved after treatment with foscarnet. Following 4 weeks of treatment, the patient was alert and oriented, following complex commands, moving all four extremities without difficulty, with no detectable neurologic deficits. He did require tracheotomy for pneumonia and pleural effusion. He was maintained on lacosamide and keppra for his seizures. EEG was repeated at 1 week, which showed no clinical or electrographic seizures. MRI brain was repeated after 4 weeks of treatment, which revealed significant interval improvement and reduction in the abnormal T2 signal abnormalities of the temporal lobe, occipital lobes, cerebellum, and brainstem. There was mild persistent T2 hyperintensity remaining in the left parahippocampal gyrus. No abnormal new enhancement was seen.

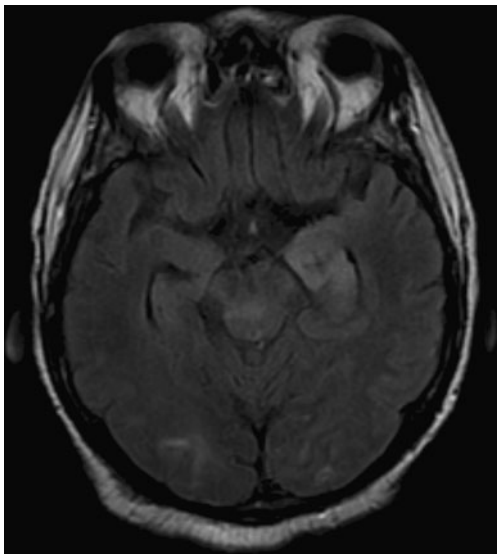

Fig. 1 MRI brain revealed multifocal T2 hyperintensities most prominent in the left mesial temporal lobe

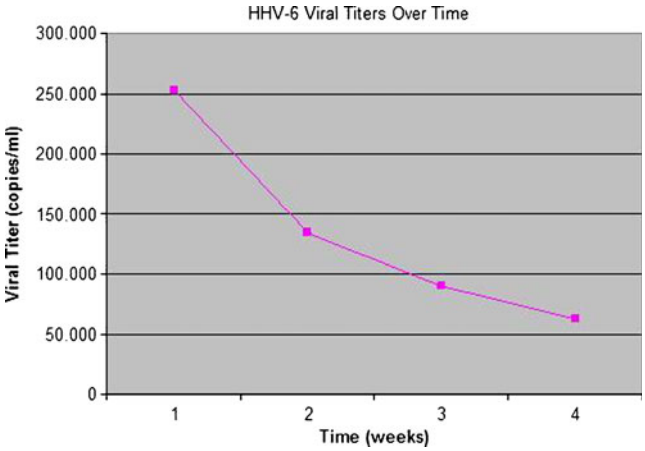

Fig. 2 This graph displays the decline of serum HHV6 virus in response to treatment with phosphonoformic acid over a 4-week period

Discussion

This is the first case of ganciclovir-resistant encephalitis in a liver transplant patient successfully treated with phosphonoformic acid. The clinical presentation of our patient included seizure and altered mental status, both of which have been well described in other cases of HHV-6 encephalitis. Interestingly, the CSF did not reveal pleocytosis despite being positive for HHV-6, likely due to the patient's overall neutropenia. MRI findings in this patient were consistent with encephalitis and further supported the diagnosis. HHV-6 encephalitis is not a benign disease, particularly in immunosuppressed patients. Overall mortality of HHV-6 encephalitis is estimated to be about 58%. In a recent study of several HHV-6 encephalitis cases, cure was identified in seven of eight patients treated appropriately. In patients not treated or treated <7 days, none of four survived (Singh and Paterson 2000).

Several in vitro studies have looked at HHV-6 susceptibility to different antiviral medications. It has been noted several times that acyclovir has limited efficacy on HHV-6 virus (Burns and Sandford 1990). A study in 2000 pointed out that ganciclovir, phosphonoformic acid, and cidofovir had similar efficacy in treated HHV-6 in vitro (Chaysavanh et al. 2000). Most preliminary studies regarding antiviral efficacy were conducted using infected T cells. Because HHV-6 virus is known to cause encephalitis, subsequent studies were designed to evaluate treatment responses in infected glial cells. Researchers found that only phosphonoformic acid and cidofovir was effective in inhibiting viral replication in HHV-6A-infected cells. This was thought to be due to the inability of these cells to produce U69 protein kinase needed to activate ganciclovir and acyclovir (Akhyani et al. 2006). Another study identified a mutation in U69 protein kinase of HHV-6A/B virus that led to

ganciclovir resistance in vitro and in vivo. It is clear from this study that patients exposed to ganciclovir have the potential to develop HHV-6 resistance (Chaysavanh et al. 2001). Similar findings have been described HCMV infection, leading to the emergence of drug-resistant HCMV (Baldanti et al. 1996).

HHV-6 resistance continues to be an emerging topic in transplant infectious disease. Although it is well described that HHV-6 causes encephalitis in post-transplant individuals, the mechanism for which resistance develops is not clear. It appears that the virus acquires resistance to gancyclovir and acyclovir by changing the U69 protein kinase needed for activation. This case highlights the importance of recognizing HHV-6 resistance in the transplant population, particularly when the patient has been exposed to ganciclovir in the past. Medical professionals may consider phosphonoformic acid or cidofovir as first-line agents in the treatment of HHV-6 encephalitis.

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