# Ganciclovir and Foscarnet Therapy of Cytomegalovirus-Associated Meningoencephalitis in a Hemodialysis Patient With Liver Transplantation: Case Report

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## ABSTRACT

Cytomegalovirus (CMV) infection in patients with liver transplantation (LT) remains a highly prevalent complication with a significant increase in morbidity and mortality. However, CMV-associated meningoencephalitis is rarely diagnosed, and treatment is very difficult. The aim of the present report is to review the experience of successful treatment with combined ganciclovir and foscarnet of CMV-associated meningoencephalitis refractory to ganciclovir alone in a hemodialysis (HD) patient after LT. A 54-year-old woman with end-stage renal disease on HD developed a seizure with loss of consciousness. She had received a liver transplant 4 months before. Blood CMV polymerase chain reaction was positive, and cerebrospinal fluid (CSF) analysis was compatible with viral meningitis. Brain magnetic resonance imaging (MRI) showed extensive dural thickening with enhancement and a round ring-like enhancement in the left centrum semiovale. She was diagnosed with CMV-associated meningoencephalitis. At that time, ganciclovir was started intravenously. After that, there were no improvements in mental state, CSF analysis, or brain MRI. Intravenous foscarnet at reduced dose was added to ganciclovir therapy. With combined ganciclovir and foscarnet, there was a slight improvement in her mental state and brain MRI.

CYTOMEGALOVIRUS (CMV) infection is the most common viral pathogen and complication after liver transplantation (LT) [1,2]. It increases morbidity and mortality in immunocompromised patients. Tissue-invasive CMV disease is a direct clinical effect of CMV after solid organ transplantation [3]. Central nervous system (CNS) disease is one result of tissue-invasive CMV disease. However, CMV meningoencephalitis is very rarely diagnosed, and most patients with CMV disease are associated with acquired immunodeficiency syndrome. The incidence of CMV meningoencephalitis after solid organ transplantation is not known. In particular, we could not find reports about CMV meningoencephalitis after LT. Currently, intravenous ganciclovir therapy is used as 1st choice to treat CMV disease. Foscarnet is a therapeutic regimen in ganciclovir-resistant CMV disease [4]. But foscarnet is a nephrotoxic drug that induces acute tubular necrosis [5]. We could not find a case report of foscarnet therapy in patients with end-stage renal disease (ESRD). The present paper describes the case of significant improvement with the use of combined ganciclovir and foscarnet for CMV-associated meningoencephalitis refractory to ganciclovir alone in an ESRD patient receiving hemodialysis (HD) after LT.

## CASE REPORT

A 54-year-old woman with ESRD on HD presented a generalized tonic-clonic seizure with loss of consciousness. She had been on regular HD 3 times per week for treatment of ESRD due to type 2 diabetes mellitus. And she had been received a liver transplant 4 months before. She had been taking 6 mg FK506 daily and 1,000 mg mycophenolate mofetil daily as the immunosuppressive regimen. There had been no sign of liver transplant rejection.

On admission, her blood pressure was 140/70 mm Hg, pulse rate 118 beats/min, respiration rate 22/min, and body temperature 37.3°C. An initial neurologic examination showed a deep-stupor mental state. Laboratory results were as follow: white blood cell count was 2,000/μL, hemoglobin 7.0 g/dL, platelet count 72,000/μL,

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blood urea nitrogen 104.4 mg/dL, creatinine 4.0 mg/dL, aspartate aminotransferase/alanine aminotransferase (AST/ALT) 54/40 IU/L, total protein 4.0 g/dL, albumin 3.0 g/dL, sodium/potassium/chloride 136/4.0/98 mEq/L, C-reactive protein 59.6 mg/dL, blood CMV polymerase chain reaction (PCR) positive, and CMV antigenemia assay 142 CMV-positive cells per 200,000 leukocytes. Owing to the deep stuporous mental state with seizure, lumbar puncture was taken to rule out CNS infection. The cerebrospinal fluid (CSF) had a high concentration of protein (over 300 mg/dL) and glucose (139 mg/dL), 32/high-power field (HPF) red blood cells (RBC), and 36/μL white blood cells (WBC) with 90% of lymphocytes. Viral, bacterial, fungal, and mycobacterial cultures were negative in CSF analysis. Brain magnetic resonance imaging (MRI) demonstrated diffuse dural enhancement and sulcal hyperintensities in the parietal lobe (Fig 1). Based on the laboratory and radiologic findings, she was diagnosed with CMV-associated meningoencephalitis and treated with intravenous (IV) ganciclovir. The ganciclovir dose was reduced by 1.25 mg/kg per day as recommended for HD patients. Also, MMF was withdrawn. On day 21 after ganciclovir treatment, serum CMV PCR and CMV antigenemia assay were negative and not detected, respectively. However, there was no change in mental status. Follow up CSF testing showed a normal concentration of glucose (68 mg/dL), high concentration of protein (>300 mg/dL), 6/HPF RBC, and 20/μL WBC with 90% of lymphocytes. Follow-up MRI showed no evidence of improvement. The serum levels of AST/ALT were 32/40 IU/dL. Ganciclovir-resistant CMV meningoencephalitis was suspected. IV foscarnet was added to the IV ganciclovir. As suggested for HD patients, the foscarnet dose was started at 50 mg/kg per day. On day 21 after combination therapy (forcarnet + ganciclovir), the patient's mental status was improving, and RBC (0–1/HPF) and WBC (8/μL with 50% of lymphocytes) showed improvement in follow-up CSF. Follow-up MRI showed improvement (Fig 2). The serum levels of AST/ALT (26/20 IU/dL) were not elevated. Serum CMV PCR and antigenemia assay were also negative and not detected. We stopped IV ganciclovir, but maintained IV foscarnet (65 mg/kg once every 2 days). Unfortunately, she died of aspiration pneumonia after nasogastric tube feeding.

## DISCUSSION

CMV can easily be experienced as one of herpes viruses that infect 60%–100% of humans [1,2]. Although clinically in immunocompetent adults CMV infection is mostly asymptomatic, this infection increases the morbidity and mortality in immunocompromised patients, such as LT recipients [1,2]. Therefore, CMV is the most common cause of infectious complications after transplantation. Direct CMV effects are classified as fever with myelosuppression (CMV syndrome) and tissue-invasive CMV disease, such as enterocolitis, pneumonitis, hepatitis, and retinitis. Indirect effects increase predisposition to opportunistic infections, allograft rejection, and death. In addition, The CMV infection occurs most commonly during the 1st 3 months after LT [6]. In the present case, the patient was diagnosed with CMV meningoencephalitis 4 months after LT. CMV encephalitis was confirmed during autopsy in 12% of HIV-infected patients and 2% of transplant recipients [7]. CMV meningoencephalitis is rarely diagnosed, especially in LT patients. Surprisingly, Ribalta et al [8] reported that CMV is present in the brain of 50.6% in 83 unselected autopsies of LT patients (control 13.8%), and 46% of the subjects with CMV in the brain had concomitant systemic CMV infection. Twenty percent of LT patients present neurologic complications such as disorientation and decreased consciousness [8]. Because brain biopsy is very difficult in LT patients with neurologic symptoms, CMV meningoencephalitis in LT recipients may be underestimated in our clinical setting.

The CSF may sometimes show neutrophilic pleocytosis, hypoglycorrhachia, and increased protein. CMV PCR in CSF has become an useful tool for recognizing CMV encephalitis. However, Holland et al [9] reported that it showed low sensitivity (33%). Another method is detection of pp65 antigen in CSF leukocytes [10,11]. CMV culture is usually negative. MRI may show enlarged ventricles and periventricular enhancement. In this case, although serum CMV PCR was positive, CMV PCR in CSF was negative. But CSF analyses found neutrophilic pleocytosis and elevated protein level, and serum CMV PCR and antigenemia were positive. The MRI finding also was consistent with CMV meningoencephalitis.

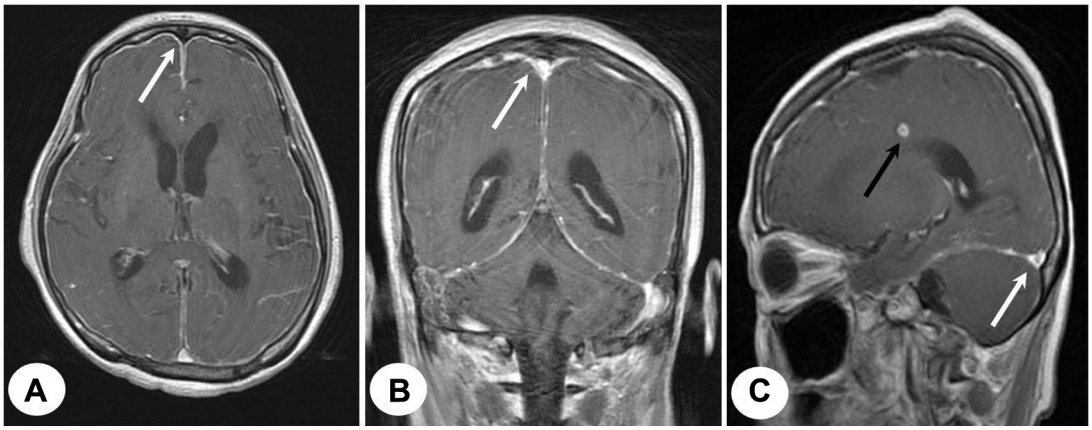


**Fig 1.** (**A**)(**B**) Magnetic resonance imaging (T1-weighted axial, coronal, and sagittal views) shows extensive dural thickening with enhancement (*white arrow*). (**C**) Round ring-like enhancement in the left centrum smiovale (*black arrow*).