Cytomegalovirus Ventriculoencephalitis in a Peripheral Blood Stem Cell Transplant Recipient

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Cytomegalovirus (CMV) infection of the CNS occurs most commonly in patients with advanced HIV infection and profound CD4 cell depletion, but it occurs rarely in transplant recipients (reviewed in [1]). Three neuropathologic entities that have been associated with overlapping clinical syndromes are described in AIDS patients with CMV infection of the CNS [1, 2]. Diffuse micronodular encephalitis, also called microglial nodule encephalitis, is a CMV infection of the gray and white matter with microglial nodules and cytomegalic changes. The clinical syndromes associated with this lesion are variable and can include anything along a spectrum from chronic dementia to acute encephalitis. CMV ventriculitis is characterized by infection of the ependymal lining of the ventricles. If the infection leads to surrounding necrosis of periventricular parenchymal tissue, it is ventriculoencephalitis [1]. Clinically, patients with ventriculoencephalitis display rapid progression of cognitive dysfunction, confusion, and mutism, often with development of cranial nerve palsies, nystagmus, ataxia. CMV polyradiculopathy is a late event in AIDS and is characterized by distal paresthesias, pain, lower-extremity weakness, and areflexia. Combined involvement of the brain and spinal cord may occur in some patients.

CNS infection due to CMV is rare in stem cell transplant recipients. We found 4 well-documented cases that had been reported [3–6], as well as 1 possible case [7]. We report here the fifth well-documented case of CNS infection due to CMV in a stem cell transplant recipient. We describe the clinical syndrome and neuropathological findings of CMV ventriculoencephalitis and analyze antiviral drug resistance mutations in the blood, compared with mutation in the CSF compartments.

Case report. Our patient was a 64-year-old CMV-seropositive man who underwent transplant of stem cells from an unrelated donor for acute myelogenous leukemia in March 2004. As part of his conditioning regimen, he was treated with pentostatin, an adenosine deaminase inhibitor, and antithymocyte globulin. After the transplant, he received mycophenolate mofetil and cyclosporin for prophylaxis of graft-versus-host disease, but cyclosporin was changed to tacrolimus because of suspected neurotoxicity. The patient developed severe graft-versus-host disease of the skin and intestines on post-transplant day 79 and received high-dose steroid therapy nearly continuously thereafter. As a result of immunosuppressive treatment, he had a CD4 cell count of 0. Reactivation of CMV infection was first detected 25 days after transplant, by PCR (viral load, 2116 copies/mL of whole blood) when treatment was stopped. The patient was treated with intravenous ganciclovir or foscarnet during the next 3 months; the choice of drug was dependent on marrow and renal function. During this period, CMV viremia decreased to low levels (<400 copies/mL of whole blood) during treatment but promptly rebounded (to a high of 28,000 copies/mL of whole blood) when treatment was stopped. The patient was hospitalized on post-transplant day 180 with nausea, vomiting, and lethargy, which were thought to be secondary to graft-versus-host disease. He became confused and exhibited bizarre behavior. Treatment with tacrolimus was stopped because of...
possible neurotoxicity, but the patient showed no improvement. The patient became increasingly withdrawn, apathetic, and then mute during the next 14 days. He was ataxic but without focal signs or abnormal reflexes. A contrast-enhanced MRI of the head showed no change from one performed 4 months previously, and no periventricular enhancement or ventricular enlargement was noted. Lumbar puncture was performed on posttransplant day 196; the results showed a WBC count of 26 cells/μL (94% lymphocytes), a protein level of 92 mg/dL, and a glucose level of 72 mg/dL. The dosage of foscarnet was increased empirically to 60 mg/kg twice per day (adjusted for diminished renal function) because of suspicion of herpesvirus encephalitis. Quantitative PCR for CMV was performed with a CSF sample as described elsewhere [8] and revealed a viral load of >1 × 10^6 copies/mL. PCR performed with a blood sample 4 days previously was positive for CMV, with a viral load of 1412 copies/mL of whole blood. PCR performed with a CSF sample was negative for herpes simplex virus, Epstein-Barr virus, varicella-zoster virus, human herpesvirus–6, and human herpesvirus–7; bacterial and fungal cultures were also negative. Ganciclovir (2.5 mg/kg twice per day, adjusted for diminished renal function) was added to treatment with foscarnet after the CSF PCR result was reported. The patient’s mental status did not improve, his renal function worsened, and he developed neutropenia. Eleven days after the lumbar puncture was performed, imaging studies revealed cavitary lesions in the lung and brain, and the patient died 3 days later.

Results. Autopsy revealed that the lining of the lateral cerebral ventricles had a fine, granular appearance with diffuse yellow discoloration. Microscopic examination of the grossly abnormal ependymal surfaces of the lateral ventricles, third and fourth ventricles, pons, and midbrain showed extensive cellular changes caused by CMV and subependymal necrosis (figure 1, left panel). Enlarged atypical cells with nuclear and cytoplasmic inclusions were found throughout the ependyma and within subependymal cells; findings of an immunohistochemical stain revealed the cause to be CMV (figure 1, right panel). The visual cortex showed areas of thrombosed vessels and/or septic emboli with subacute infarction due to aspergillosis. The spinal cord was unremarkable. No CMV infection was found outside the brain. The right upper lobe of the lung had a 6-cm cavitary lesion. Examination of the lung sections revealed multifocal abscesses with parenchymal hyphae, and cultures grew Aspergillus fumigatus. Angioinvasive aspergillosis was also found in the kidneys.

Resistance to currently available antiviral drugs used to treat CMV infection may result from mutations in either the UL97 or the UL54 genes, or both. UL97 encodes the viral protein kinase responsible for the initial phosphorylation of ganciclovir and cidofovir. UL54 encodes the DNA polymerase, which is the target of ganciclovir, cidofovir, and foscarnet. To determine whether resistance to antiviral therapy played a role in this patient’s fatal case of encephalitis, we sequenced these genes [9] from DNA isolated from the CSF and 2 independent blood
samples obtained within 10 days of when the CSF sample was obtained. No mutations in UL97 were found in DNA from either the CSF or peripheral blood samples. DNA from both blood samples and the CSF had polymorphisms in UL54 (Ala885Thr and Ser897Leu) that do not confer drug resistance. Both blood samples had a mutation in UL54 (Val278Ala) in a codon that has previously been shown to confer resistance to foscarnet and ganciclovir (4.1-fold and 2.4-fold, respectively, compared with wild type) [10]. No resistance mutations were found in CSF DNA.

**Discussion.** Evaluation of the course of this patient’s illness and comparison with the 4 well-documented cases [3–6] raise several important points regarding CMV infection of the CNS in stem cell transplant recipients. Although pathologic findings were not described in 3 of the prior cases, the clinical syndromes suggest that 3 of the 4 patients had CMV ventriculoencephalitis, which 1 of them may have developed from progression of CMV polyradiculopathy [5]. This neuropathologic entity is common in advanced AIDS but not in transplant recipients [1]. Three of the 4 previous stem cell recipients with CMV infection of the CNS resemble patients with AIDS-associated CMV encephalitis in that there is evidence of either high-level viremia, retinitis, or extraneural involvement. In contrast, our patient had low-level peripheral viremia during treatment, and no evidence of invasive CMV disease outside the brain was found during autopsy. Interestingly, one other stem cell transplant recipient had evidence of compartmentalization of CMV infection in that there was progression of encephalitis despite a marked decline in peripheral blood CMV antigenemia when treatment was changed because of suspected drug resistance [6].

Genotypic and phenotypic analysis of drug resistance in CMV from these 5 patients reveals that resistance mutations may play a role in pathogenesis, but progressive encephalitis unfortunately appears to be the typical outcome even when viral strains in the CNS are susceptible to antiviral drugs. Sequencing of both UL97 and UL54 was performed with the CNS isolates obtained from 4 of the 5 case patients. Two isolates (from [4] and the current report) showed no resistance mutations, 1 had a mutation only in UL97, which conferred ganciclovir resistance [6], and 1 had a mutation only in UL54, which conferred resistance to ganciclovir and cidofovir [3]. Sequence data from our patient and from a previous case [4] demonstrate that viral strains may be compartmentalized. In our patient, CMV mutations were present only in peripheral blood, whereas no mutation was detected in the CSF. Similarly, Hamprecht et al. [4] found no resistance mutations in viral DNA from the CNS sample of their patient, whereas 2 non-dominant populations of resistant virus strains were documented in plasma and other sites. The data show that analysis of peripheral sites cannot predict the genotype and phenotype of virus strains in the CNS. The implications for antiviral therapy remain to be determined, but these findings suggest that the possibility of compartmentalization and different resistance patterns at distinct sites should be considered in these severely immunocompromised patients.

Quantitation of CMV virus in CSF has not been reported previously in stem cell transplant recipients. A striking feature in our patient was the very high viral load in CSF (>10⁶ copies/mL) compared with the viral load in peripheral blood. This viral load is even higher than the levels of CMV DNA found in CMV reported previously in AIDS patients with ventriculoencephalitis [11] and likely reflects the extensive viral replication observed in ependymal cells lining the ventricles and in periventricular cells. The absence of resistance mutations in the CSF suggests that a compartmentalized, drug-resistant virus was not a significant factor in treatment failure. However, concentrations as high as 6 μM of ganciclovir (1.53 μg/mL) and 400 μM of foscarnet (120 μg/mL) may be required for the inhibition of drug-susceptible strains. These concentrations are difficult to achieve and sustain in CSF [12–14]. Therefore, inadequate drug penetration, as well as the severely immunocompromised state of the patient, may have contributed to treatment failure. Recent data suggest that some resistance mutations in UL97 and UL54 decrease the replicative capacity of the mutant CMV compared with wild-type CMV [15]. If this is correct, it may also have contributed to the extensive replication of wild-type virus in the CSF compared with the resistant mutant virus in peripheral blood.

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**References**


