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Case report

Human immunodeficiency virus–associated cytomegalovirus infection with multiple small vessel cerebral infarcts in the setting of early immune reconstitution

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Cytomegalovirus (CMV) infection is an important cause of neurologic disease in the context of advanced human immunodeficiency virus (HIV) infection and is recognized as a cause of immune reconstitution inflammatory syndrome (IRIS) after initiation of highly active antiretroviral therapy (HAART). Central nervous system vasculitis secondary to CMV has only rarely been described in the context of HIV, despite the established ability of CMV to infect microvascular endothelial cells in the brain. However, we report a case that demonstrates the association between CMV and multiple small vessel cerebral infarct lesions after initiation of HAART. *Journal of NeuroVirology* (2010) **16,** 179–184.

Keywords: AIDS; cytomegalovirus; HIV

Case

A 38-year-old male with human immunodeficiency virus (HIV) presented with left-sided weakness approximately 4 weeks after initiating highly active antiretroviral therapy (HAART). Just prior to beginning treatment, he was antiretroviral naïve with a CD4+ T-cell count of 1 cell/μl (0%) and plasma HIV RNA level of >500,000 copies/ml. HIV genotyping showed multiple resistance mutations (D67N and K219Q of the reverse transcriptase inhibitor class and L10I, M36I, I84V, and L90M of the protease inhibitor class). He was started on a regimen of darunavir/ritonavir, efavirenz, and tenofovir/emtricitabine. Two weeks later, he presented with visual change of the left eye that he described as a "shroud" sensation. Dilated funduscopic exam with the assistance of the ophthalmology service showed patches of retinal whitening and intraretinal hemorrhage encroaching on the fovea. Given that the patient was seropositive for cytomegalovirus (CMV) immunoglobulin G (IgG), these findings were felt to be highly consistent with CMV retinitis. The patient was continued on his antiretroviral regimen and was started on intravitreal foscarnet injections as well as oral valganciclovir. After approximately 2 weeks of anti-CMV therapy, he began to notice weakness in his left leg. Over the next 5 days, this progressed to a left foot drop as well as weakened grip strength of the left hand. The patient was admitted to the hospital for further workup. Plasma HIV RNA level had decreased to 32,700 copies/ml and CD4+ T-cell count had risen to 23 cells/μl (2%). Magnetic resonance imaging of the brain showed multiple areas of abnormal restricted diffusion and corresponding dark signal on apparent diffusion coefficient (ADC) mapping. These areas included the left cervicomedullary junction, the right ventral medulla, and a large area involving the right globus pallidus, anterior internal capsule, and caudate head (see Figure 1). The findings were consistent with acute to early subacute infarctions in multiple small vessel territories that were suggestive of vasculitis.

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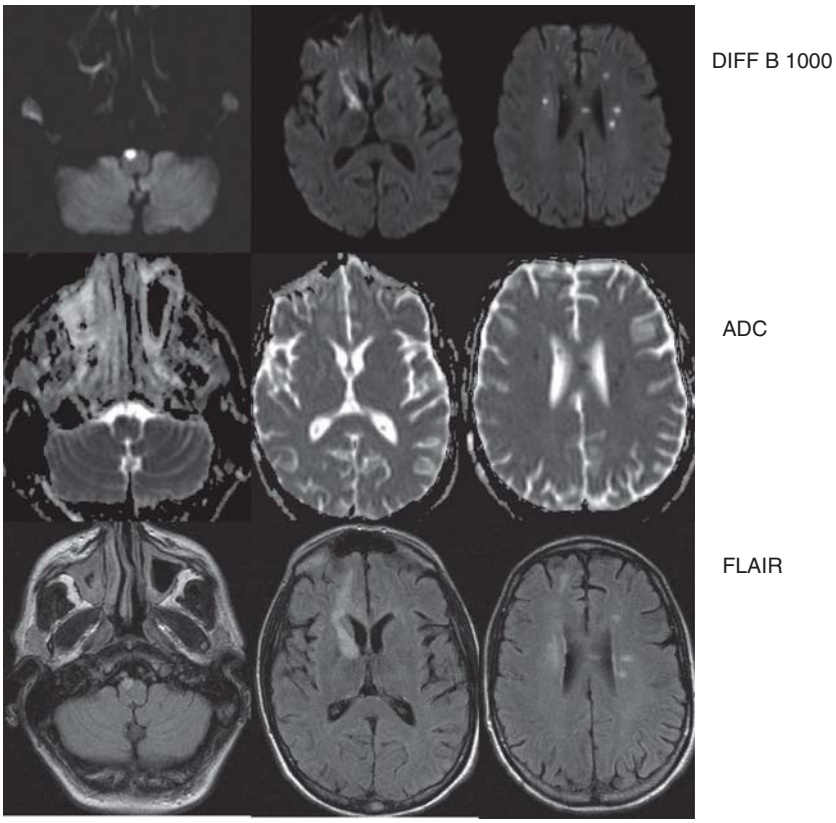

Figure 1 Magnetic resonance imaging shows congruent abnormalities on diffusion and T2 consistent with small penetrating end artery infarction. The image detail intensity strongly suggests a monophasic event.

Serum rapid plasma reagin (RPR) was negative. A repeat RPR test, which included testing for the prozone phenomenon was also negative. Antinuclear antibody (ANA) screening, which included testing for anti–double-stranded DNA was negative, as was testing for antineutrophil cytoplasmic antibodies (ANCAs). Complement levels were within normal limits and testing for cryoglobulinemia was negative. Urine drug screen was negative. Blood cultures for bacterial, fungal, and acid-fast bacilli organisms were negative. Electrocardiogram was within normal limits and transthoracic echocardiography (TTE) showed normal heart chambers with left ventricular ejection fraction of 60%. Heart valves were normal in appearance with no dysfunction except for mild mitral regurgitation.

Cerebrospinal fluid (CSF) testing showed a white blood cell count of 23 cells/μl (76% lymphocytes, 23% monocytes) and red blood cell count of 0 cells/μl. CSF protein and glucose were within normal limits. Cytomegalovirus DNA by polymerase chain reaction (PCR) was positive from the CSF. Other CSF studies were negative, including VDRL (Venereal Disease Research Laboratory) test, cryptococcal antigen, Epstein-barr virus DNA, herpes simplex virus DNA, varicella-zoster virus DNA, JC virus DNA, and toxoplasma antibodies. CSF bacterial, fungal, and acid-fast bacilli cultures were also negative. Funduscopic exam on admission showed persistent CMV lesions of the left eye with the interval development of active vitritis that was consistent with CMV immune restoration inflammatory syndrome (IRIS). As per Infectious Diseases Society of America (IDSA) guidelines, the patient was started on combination therapy for central nervous system CMV infection with intravenous ganciclovir and foscarnet. Due to concern over possible vasculitis, the patient underwent both computed tomography angiogram (CTA) and magnetic resonance angiogram (MRA) of the head within 1 week of the initial magnetic resonance imaging (MRI). However, both of these studies were within normal limits. He received 14 days of therapy with ganciclovir and foscarnet, over which time his weakness and gait improved significantly. A repeat MRI of the brain after intravenous therapy showed interval evolution of infarctions in the bilateral periventricular white matter, right internal capsule, and right medulla (see Figures 2 and 3). On discharge, his antiretroviral regimen was continued as was valganciclovir 900 mg PO twice daily. Six months after discharge, his weakness and gait abnormality

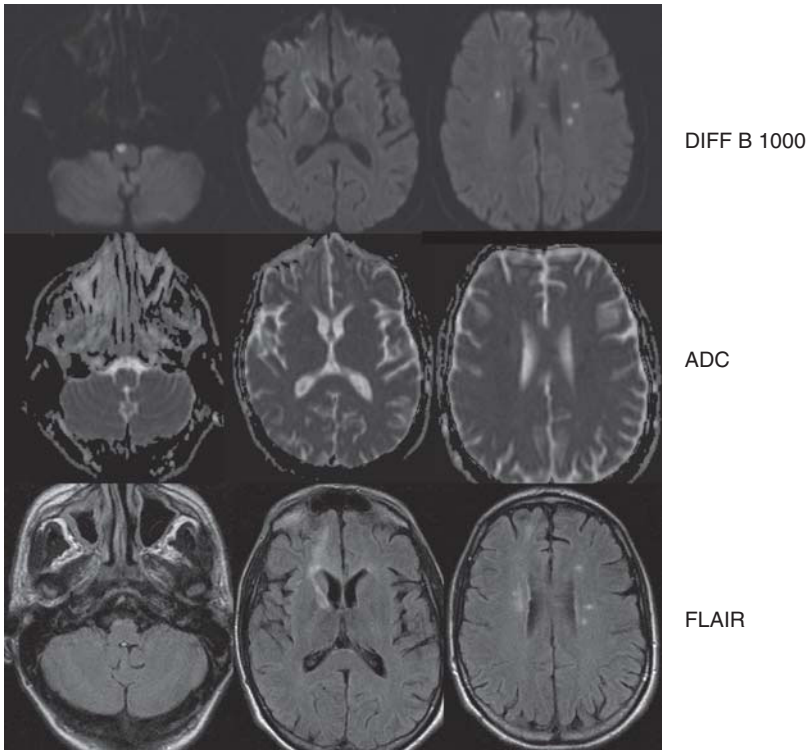

Figure 2 Magnetic resonance imaging shows interval evolution with decreasing conspicuity of the diffusion abnormality especially the ADC map. There are no new areas of suspected infarction again supporting a monophasic process.

had resolved while on HAART and maintenance valganciclovir.

Discussion

End-organ CMV disease represents a Centers for Disease Control and Prevention (CDC) category C acquired immunodeficiency syndrome (AIDS)-defining illness (Crowe *et al,* 1991). Retinal and central nervous system (CNS) involvement are among the most common forms of AIDS-associated CMV disease. Clinicopathologic manifestations of AIDS-associated CMV disease of the CNS have mainly been described as either micronodular encephalitis or necrotizing ventriculoencephalitis (Arribas *et al,* 1996; Morgello *et al,* 1987). The role of cytomegalovirus in the development of vascular disease has been controversial. A prospective study of healthy men did not find an association between CMV seropositivity and either stroke or myocardial infarction (Ridker *et al,* 1998). However, the presence of CMV has been identified in vascular endothelial cells *in vivo* (Sinzger *et al,* 1995). CMV has been shown to infect aortic endothelial cells, producing a chronic noncytolytic infection (Fish *et al,* 1998). This may be a source of latency for CMV with subsequent dissemination from this site occurring within monocytes (Waldman *et al,* 1995). The presence of CMV in the microvascular endothelial cells of the brain has also been demonstrated and is associated with cytolytic infection (Fish *et al,* 1998).

Prior to the HIV epidemic, isolated cases of CNS vasculitis related to CMV infection were reported in the setting of profound immunosuppression from antineoplastic medications (Koeppen *et al,* 1981). In the pre-HAART era of the HIV epidemic, CNS vasculitis from CMV was reported infrequently in HIV-infected individuals with severely diminished CD4+ T-cell counts. Many of these cases were found post mortem and did not correlate with clinical syndromes (Klatt and Shibata, 1988). In rare cases, patients presented with CMV disease of the CNS manifesting clinically and radiographically with vascular infarcts (Kieburtz *et al,* 1993). In our case, we believe that this presentation of CMV represents a form of IRIS. The decline in plasma HIV RNA level was consistent with recent definitions of IRIS (Shelburne *et al,* 2002) and the presence of inflammation was demonstrated by CSF pleocytosis and vitritis. Current understanding of IRIS suggests that immunopathology results from the restoration of protective pathogen-specific cellular immune responses after initiation of HAART. There is a high concentration of CD8+ cytotoxic T-lymphocytes in this reponse, particularly in IRIS syndromes

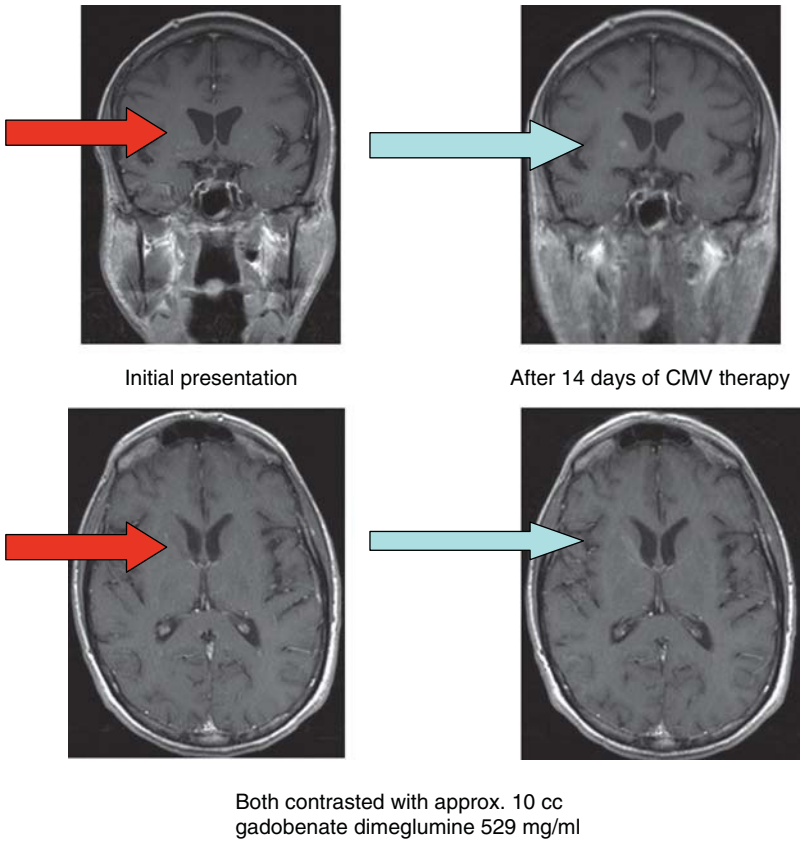

Figure 3 The lack of enhancement on intitial presentation (red arrow) is consistent with acute infarction and not abscess, whereas the development of enhancement after 14 days of CMV therapy (blue arrow) suggest evolving infarction.

driven by viruses (French, 2009). One example of how this process might result in CNS vasculitis is varicella-zoster virus (VZV). In cases of CNS vasculitis from VZV in non–HIV-infected hosts, VZV antigens and DNA are found in the intima of cerebral arteries (Gilden *et al,* 1996). Not surprisingly, VZV has subsequently been recognized as an etiology for CNS IRIS vasculitis (Patel *et al,* 2006). There have also been reports of CNS IRIS vasculopathies without identification of a specific infectious agent. Cerebral vasculopathy with aneurysm formation after initiation of HAART has been described in children and young adults (Bonkowsky *et al,* 2002; Kossorotoff *et al,* 2006). Primary CNS vasculitis has also been reported as a form of IRIS (Melica *et al,* 2009). Given the fact that CMV can establish itself in the endothelial cells of the brain, it is somewhat surprising that clinically apparent cerebral infarcts from CMV have not been described with immune reconstitution in the HAART era.

The differential diagnosis for cerebral ischemia and stroke in the setting of HIV infection is broad and HIV-infected patients appear to be at higher risk (Dobbs and Berger, 2009). HIV-infected patients have accelerated atherosclerosis. Hypercoagulability has also been described in the setting of HIV. Additionally, infectious etiologies such as VZV and syphilis have produced CNS vasculitis syndromes in HIV-infected patients. In our case, the radiographic presentation was that of monophasic, small artery infarcts that are most consistent with vasculitis. Although less invasive angiographic studies in this case did not definitively show vasculitis, conventional cerebral angiography was not pursued due to high clinical suspicion and the clinical improvement of the patient. This was also influenced by the fact that conventional angiography is known to lack sensitivity in the setting of CNS vasculitis (Duna and Calabrese, 1995). Angiography studies also have low sensitivity for the detection of abnormalities in the setting of infectious vasculopathies such as VZV (Nagel *et al,* 2008). The gold standard for the diagnosis of CMV vasculitis is brain biopsy. However, given the presence CMV disease in this case, the improvement of the patient's condition on anti-CMV therapy, and the potential risks of the procedure, it was not felt necessary to pursue brain biopsy in the care of this particular patient.

With regards to treatment, although the initial worsening of symptoms despite treatment with valganciclovir is troubling, it is not without precedent. There have been cases of HIV-associated CMV retinitis in which CMV encephalitis has developed despite ganciclovir therapy (Berman and Kim, 1994). For

this reason and because of a small study showing the efficacy of dual therapy with intravenous ganciclovir plus foscarnet (Anduze-Faris *et al,* 2000), the IDSA now recommends this combination for the treatment of CMV disease of the CNS (Tunkel *et al,* 2008). Despite the symptoms of IRIS, the administration of HAART in this patient with invasive CMV disease was likely life-saving. In the pre-HAART era, the prognosis of patients with AIDS and invasive CMV disease was poor, particularly for those patients with CMV encephalitis (Anduze-Faris *et al,* 2000). However, the prognosis for HIV-infected patients with invasive CMV disease has clearly improved with HAART (Kofteridis *et al,* 2007; Sklar *et al,* 2004). Therefore, we believe that continuation of HAART in this case was essential for the patient's overall improvement. In cases of primary CNS vasculitis, the standard of care treatment that is typically used even in the setting of HIV infection is immunosuppressive therapy (Melica *et al,* 2009). However, the role of immunosuppressants such as corticosteroids in the setting of infectious CNS vasculitis in HIV-infected patients is less defined. Although certain case reports suggest that corticosteroids may be beneficial in this setting (Newsome and Nath, 2009), definitive data on their use is lacking. Overall, the use of corticosteroids in the setting of IRIS may be beneficial for symptoms, but this strategy has not been studied rigorously (French, 2009). Systemic corticosteroids in our case were not used due to clinical improvement with systemic antivirals and continuation of HAART, but may have been considered if the condition of the patient had worsened despite these therapies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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