Recent reports suggest that human immunodeficiency virus (HIV)–associated progressive multifocal leukoencephalopathy (PML) may improve with highly active antiretroviral therapy (HAART). We observed three patients who developed PML while receiving HAART. All patients received HAART for 4–11 months and had low plasma levels of HIV-1 RNA before the onset of symptoms of PML. Antiretroviral therapy was changed in two patients, and their plasma HIV-1 RNA levels declined significantly. Despite this virologic response, PML did not improve in these patients. The third patient’s HIV-1 RNA level became undetectable while he was receiving HAART, and his symptoms of PML improved after the addition of interferon α. Our observations suggest that PML can develop in patients who have shown clinical response to HAART. Furthermore, PML may not improve despite an adequate virologic response to HAART. Definitive therapy is still needed for PML.

Progressive multifocal leukoencephalopathy (PML) is an infection of the white matter of the CNS that is usually fatal. There is no proven curative treatment [1]. Recent case series of HIV-associated PML suggest that protease inhibitor–based highly active antiretroviral therapy (HAART) may lengthen survival and improve neurological outcome [2–8]. Recently, we observed three patients with PML that developed in the presence of HAART.

Case Reports

Case 1. A 51-year-old man presented with dysarthria and weakness of the left arm and leg. One year prior, the patient began taking stavudine, 40 mg twice daily; lamivudine, 150 mg twice daily; and saquinavir soft-gel, 600 mg three times daily. One month later, the patient’s plasma HIV-1 RNA level was 8,003 copies/mL and his CD4+ lymphocyte count was 175/mm³. Eleven months later, the patient developed weakness of the right upper and lower extremities and dysarthria. MRI of the brain showed nonenhancing lesion of the left cerebellar hemisphere. CSF testing by PCR showed positive results for JC virus. The antiretroviral regimen was changed to didanosine, 200 mg twice daily; lamivudine, 150 mg twice daily; indinavir, 800 mg thrice daily; and nevirapine, 200 mg twice daily. Two months later, the plasma HIV-1 RNA level was 409 copies/mL and his CD4+ lymphocyte count was 656/mm³. Despite the immunologic and virologic improvement, the patient had neurological deterioration and died 2 months later.

Case 2. A 45-year-old man presented with several weeks of frontal headaches, grand mal seizures, diplopia, and blurred vision. He was initially treated with zidovudine, 200 mg three times daily; lamivudine, 150 mg twice daily; and indinavir, 800 mg three times daily. His plasma HIV-1 RNA level was 27,522 copies/mL when this therapy was begun. Zidovudine was changed to stavudine, 40 mg twice daily, because of the patient’s intolerance to zidovudine. A plasma HIV-1 RNA measurement done 8 months into therapy was 1,803 copies/mL and his CD4+ lymphocyte count was 100/mm³. One month later, he noted the onset of frontal headaches and then had two grand mal seizures followed by diplopia and blurred vision. MRI of the brain revealed a new ring enhancing lesion of the left parietal lobe that showed PML on histologic analysis. Antiretroviral treatment was changed to didanosine, 200 mg twice daily; nevirapine, 200 mg twice daily; and saquinavir, 400 mg twice daily; ritonavir, 400 mg twice daily; and saquinavir, 400 mg twice daily. The HIV-1 RNA decreased to undetectable levels and his CD4+ lymphocyte count rose to 201/mm³ within 2 months. However, the neurological symptoms continued, and he died 1 month later.

Case 3. A 37-year-old man presented with blurred vision and progressive weakness of the extremities. Nine months before presentation, he began treatment with stavudine, 40 mg twice daily; lamivudine, 150 mg twice daily; and indi-
of any proven curative therapy, HAART is currently considered needed. There may be several reasons why PML can develop and/or progress despite the use of HAART. Clearly, nonadherence to HAART is one possibility. Our patients had detectable levels of HIV before the diagnosis of PML, which is suggestive of suboptimal adherence. However, adherence after the diagnosis of PML was good, since each of our patients had a virologic and immunologic response temporally associated with the use of antiretrovirals. Another possible explanation is that PML may develop in patients with a previously established CNS infection with JC virus that antedates treatment with HAART. In this scenario, PML would develop regardless of any subsequent virologic response to HAART.

Discussion

PML is a devastating disease that is usually fatal in advanced HIV infection. There have been a number of case reports of agents with putative efficacy against PML [1]. However, there are no controlled studies demonstrating curative therapy for PML. Recently, there have been several reports of improvement in PML with treatment with HAART that usually includes a protease inhibitor [2–8]. In an ongoing prospective observational study of PML, the use of HAART was associated with a median survival of >12 months, compared with survival of <4 months without treatment [4]. Gasnault et al. [5] similarly reported a median survival of 15.5 months with the use of HAART in patients with AIDS-related PML. In the absence of any proven curative therapy, HAART is currently considered the standard of care for PML.

Our patients demonstrate that not only can PML develop while using HAART, but that a good virologic response to antiretroviral therapy does not ensure the resolution of symptoms of PML. All of our patients had a >1 log decline in HIV-1 RNA levels after they were diagnosed with PML. The one patient who showed clinical improvement also received treatment with IFN-α. Although these observations are clearly anecdotal, they suggest that HAART may not prevent PML in all cases and may not be effective in all patients who develop PML while taking HAART. Piliero et al. [9] recently reported similar findings. They described a patient who received HAART for 3 weeks before the onset of PML and another patient who had not received HAART before the onset of PML. Both were treated with HAART plus IFN-α2b and peptide T. Neither patient improved despite having a virologic response to HAART. Finally, we have recently observed two additional patients (data not shown) who developed PML while receiving HAART, both of whom had very low HIV-1 RNA levels.

References