Acute Primary Human Immunodeficiency Virus Type 1 Infection in a Patient with Concomitant Cytomegalovirus Encephalitis

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We report what we believe is the first case of primary human immunodeficiency virus type 1 (HIV-1) infection and simultaneous cytomegalovirus (CMV) encephalitis, which was confirmed by detection of CMV DNA in the patient's cerebrospinal fluid with use of the polymerase chain reaction. This coinfection had an unusual course, and the patient's clinical status deteriorated despite administration of combination antiretroviral therapy. The patient responded clinically only after therapy for CMV infection was added to his combination antiretroviral regimen. An atypical course and duration of symptomatic primary HIV-1 infection should suggest a possible coincident infection with other opportunistic agents that are normally expected to cause disease later in the course of HIV-1 infection. Current recommendations from the Centers for Disease Control and Prevention list CMV encephalitis as an AIDS-defining event.

Primary HIV-1 infection results in an acute clinical illness of varying severity, acute retroviral syndrome, in 18%-70% of individuals newly infected with HIV-1 [1, 2]. Symptomatic primary HIV-1 infection may present as a flu-like illness; symptoms include fever, malaise, myalgias, arthralgias, rash, headache, lethargy, sore throat, nausea, vomiting, diarrhea, and weight loss [3-5]. This mononucleosis-like illness typically lasts 1-6 weeks and is not associated with any residual deficits [5-9]. Over the ensuing 8-12 years, most HIV-1 infections progress to AIDS [10]. Individuals with severe, prolonged primary HIV-1 infection usually have a higher titer of plasma virus during the acute infection and develop AIDS more rapidly than do those whose primary HIV-1 infection is asymptomatic [2, 6, 11, 12].

We describe a patient with acute cytomegalovirus (CMV) encephalitis and primary HIV-1 infection. He responded clinically only after therapy for CMV infection was added to his combination antiretroviral regimen.

Methods

Serological analysis. Serum antibodies for HIV-1 were detected using the Recombigen (ENV and GAG) HIV-1 EIA kit (Cambridge Biotech Corporation, Worcester, MA) per the package insert. The result was confirmed by western blot assay (Bio Rad Laboratories, Hercules, CA). HIV-1 p24 antigen in serum was detected with use of the Coulter HIV-1 p24 Antigen Assay Kit (Coulter Immunology, Hialeah, FL) after dissociation of immune complexes by the Coulter ICD-Prep Kit. Serum antibodies to HIV-1 p24 antigen were detected using the Coulter HIV-1 p24 Antibody Kit.

IgM antibodies to CMV were detected with use of ELISA kits (BioWhittaker, Walkersville, MD), and IgG antibodies to CMV were also detected with use of ELISA kits (Clark Laboratories, Jamestown, NY).

CMV culture. Samples of blood and urine were cultured at Corning Clinical Laboratories (Teterboro, NJ).

PCR analysis. The copy number of HIV-1 RNA in plasma was determined by Corning Clinical Laboratories with use of the primer pair Bio-SK462–Bio-SK431 from the gag region, according to the procedure developed by Roche Molecular Systems, Roche Diagnostic Systems (Branchburg, NJ). CMV DNA was detected in CSF with use of two primer sets in separate PCR assays.

The first set of primers, designated CMV L and CMV R, yielded a product of 100 base pairs [13], and the second set, designated LA1 and LA2, yielded a product of 139 base pairs [14]. By using both primers, the sensitivity associated with detection of culturable CMV types was 100% [14]. CSF was assayed undiluted and after a 10-fold dilution with sterile water. Five microliters of CSF were heated in a microwave oven for 8 minutes at 550 watts. Twenty microliters of a PCR Master Reaction Mix containing AmpliTaq DNA polymerase (Perkin-Elmer Cetus, Norwalk, CT) and a single set of the primers was added.

The second set of primers was assayed separately in a similar mixture. Samples were subjected to 40 temperature cycles (25 seconds at 94°C, 15 seconds at 60°C, and 60 seconds at 72°C) in a Perkin-Elmer Cetus 9600 thermocycler, and the products were analyzed by agarose gel electrophoresis and ethidium bromide staining. To detect potential interfering substances, samples of undiluted CSF and diluted CSF were mixed with an equal volume of culture medium known to contain CMV, and both samples were assayed in the same manner.
Table 1. Pertinent laboratory results for a patient with symptomatic primary HIV-1 infection and cytomegalovirus encephalitis.

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<tr>
<td>ELISA</td>
<td>Negative</td>
<td>Positive</td>
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<td>Western blot</td>
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<td>ICD p24 antigen (pg/mL)</td>
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<td>Antibodies to p24 antigen</td>
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<td>HIV-1 RNA (copies/mL)</td>
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<td>CD8 cells/mm³</td>
<td>749</td>
<td>458</td>
<td>1,730</td>
<td>67</td>
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<td>19</td>
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<td>CD8 cells/mm³</td>
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<td>CD4/CD8 ratio</td>
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<td>IgM antibodies to CMV (EU/mL)*</td>
<td>84</td>
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<td>IgG antibodies to CMV (ISR)†</td>
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<td>PCR for CMV DNA‡</td>
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NOTE. CMV = cytomegalovirus; EU = enzyme units; ISR = immune status ratio.

* Upper limit of normal, 0.89.
† Upper limit of normal, 0.90.
‡ See figure 1.

Case Report

A 26-year-old homosexual male was hospitalized on 6 October 1994 because of a 3-week history of fever, chills, headache, abdominal pain, vomiting, and severe generalized weakness. His medical history was unremarkable, and he had repeatedly tested negative for antibodies to HIV-1. He had had one episode of unprotected receptive anal intercourse 2 weeks before the onset of his symptoms. On admission, he was acutely ill with nausea and vomiting, and his temperature was 104°F. Mild right upper quadrant tenderness was present.

Laboratory tests revealed the following values: WBC count, 6,100/mm³ with 15% mature neutrophils, 16% band forms, and 64% lymphocytes; platelet count, 61,000/mm³; total bilirubin level, 1.2 mg/dL; aspartate aminotransferase, 1,814 U/L; alanine aminotransferase, 1,962 U/L; and alkaline phosphatase, 144 U/L. Routine blood cultures and acute serological markers for hepatitis A virus and hepatitis B virus were negative.

An ELISA for antibodies to HIV-1 was negative (table 1). The level of IgM antibodies to CMV was 85 EU (enzyme units)/mL; the level of IgG antibodies to CMV was 2.79 immune status ratio. A chest radiograph was clear. The patient was treated empirically with oral cefuroxime (250 mg b.i.d.) for a presumptive bacterial infection. At discharge from the hospital after 7 days of treatment, he was still febrile (temperature, 101°F), but his abdominal pain had resolved. He was instructed to complete the 10-day course of oral cefuroxime.

Lack of response to cefuroxime therapy and recurrence of the symptoms (daily fevers [temperature to 104°F], severe generalized headaches, and vomiting several times a day) prompted the patient to request a repeat test for HIV. An ELISA was now positive for antibodies to HIV-1, and seroconversion was confirmed by western blot assay; antibodies to p24 antigen and p31 antigen were present, as were antibodies to antigen gp120 and antigen gp160 (table 1). The CD4 lymphocyte count was 749/mm³ (19%).

Four weeks later, when he first presented to our clinic, he had a 23-pound weight loss, a maculopapular rash on his body, and weakness of the right arm. On the presumption that his illness was due to severe primary HIV-1 infection with inflammatory changes in the brain, which resulted in the development and progression of the neurological signs, treatment with zidovudine (600 mg/d), zalcitabine (2.25 mg/d), and prednisolone (30 mg/d) was initiated. His fever, nausea, and vomiting persisted after 21 days of treatment, as did his right arm weakness. The prednisolone therapy was discontinued, and he was rehospitalized for further diagnostic evaluation.

Laboratory studies on admission revealed that the platelet count had increased to 97,000/mm³ and that the WBC count was 3,900/mm³ with persistent lymphocytosis (55% lymphocytes). Multiple blood cultures were negative for bacteria, mycobacteria, and fungi. Two cultures of blood and urine were negative for CMV. Serological analyses for other microbial agents, including Treponema pallidum and Borrelia burgdorferi, were negative. The liver enzyme levels had returned to normal. The absolute CD4 and CD8 cell counts were 458/mm³ (17.6%) and 1,730/mm³ (66.5%), respectively. The plasma level of HIV-1 RNA was 121,150 copies per milliliter. p24 antigen after immune complex dissociation was negative, and the titer of antibodies to p24 antigen was positive at 1:25.

Findings on esophagogastroduodenoscopy were negative. Examination of a skin biopsy specimen revealed focal
lymphohistiocytic proliferation consistent with granuloma annulare. The neurological deficit progressed to involve the patient’s right leg. Findings on an MRI of the head were normal. Analysis of the CSF showed no cells, a protein level of 31 mg/dL, and a glucose concentration of 49.2 mg/dL. An India ink smear of the CSF for Cryptococcus neoformans was negative, as was a Venereal Disease Research Laboratory test.

PCR performed on clarified CSF was strongly positive for CMV DNA in undiluted CSF and was negative after a 10-fold dilution (figure 1). Panel a, lane B, shows that an amplified band of ~139 base pairs was present; this was the size expected for the amplified product for the oligomer set complementary to the late antigen gp64 DNA [14]. This positive result was confirmed with use of primers CMV L and CMV R [13]; these primers yielded a product of 100 base pairs (results not shown). A diagnosis of CMV encephalitis was made.

The patient was initially treated with intravenous ganciclovir at a dosage of 5 mg/kg b.i.d. Within 48 hours of the initiation of treatment, he became afebrile, his headache diminished for the first time in 4 months, and his nausea and vomiting abated. Even though his condition continued to improve symptomatically, he developed a drug fever at the end of the second week of therapy. On day 14, therapy with ganciclovir was discontinued, and intravenous foscarnet was substituted at a dosage of 90 mg/kg b.i.d. The right-sided weakness continued to resolve, but he still needed support for ambulation. The rash also slowly resolved.

After a 3-month course of daily foscarnet and combination antiretroviral therapy, the patient had gained 15 pounds and was able to resume daily household activities. A repeated PCR analysis revealed that his CSF was negative for CMV DNA (figure 1; panel b, lanes B and C). His absolute CD4 cell count had normalized and was now 1,270/mm³ (37.1%), but his CD8 cell count remained elevated at 1,427/mm³ (41.7%). The level of HIV RNA in plasma had decreased markedly to 13,900 copies/mL (table 1).

Foscarnet therapy was discontinued, but the patient continued to receive combination antiretroviral therapy. Ten months
after the onset of his illness and 3 months after therapy with foscarnet was discontinued, he required no support for ambulation.

Discussion

Cofactors such as a second infecting agent may increase the probability and severity of a symptomatic primary HIV-1 infection. In prior reports, CMV coinfection was believed to be responsible for prolonging and increasing the severity of primary HIV-1 infection [15–17]. We have described a patient whose primary HIV-1 infection was complicated by concomitant CMV encephalitis. The acute retroviral syndrome was atypical because of the persistence of symptoms for 3–4 months, the presence of focal neurological signs, and the presence of cutaneous granuloma annulare.

Either HIV or CMV could have caused our patient’s initial lymphocytosis, thrombocytopenia, and hepatitis. The role—if any—of HIV in the pathogenesis of his encephalitis remains unclear. He was never severely immunosuppressed, and it is well known that encephalitis may complicate a primary CMV infection in immunocompetent adults [18,19].

Eight weeks after the onset of his illness, cultures of blood and urine were negative for CMV, suggesting sporadic shedding of virus or insensitivity of the cultures. However, three elements suggest that acute CMV infection, in addition to primary HIV-1 infection, was key to his illness: the presence of serum IgM antibodies to CMV; a strongly positive PCR result, indicating the presence of CMV DNA in his CSF; and the fact that symptomatic relief occurred only after treatment with ganciclovir was initiated. Before therapy for CMV infection was started, his illness had continued to progress despite administration of zidovudine and zalcitabine for 4 weeks.

CMV-related neurological diseases are frequently discovered only at autopsy. As the clinical manifestations may be nonspecific, a laboratory method has been urgently needed to reliably diagnose active CMV disease of the CNS ante mortem [20]. Detection of CMV DNA in CSF with use of PCR appears to be that method; PCR has become both sensitive and specific for detecting CMV infection of the CNS [21–23].

Now that a reliable test is available, it remains to be determined if early treatment with ganciclovir or foscarnet will prove useful for CMV-related neurological complications. Our patient responded only after the initiation of therapy for CMV infection. In addition to symptomatic improvement in his condition, his plasma viral load (measured by copies of HIV-1 RNA per milliliter) decreased markedly, and his CD4 cell counts increased to normal. The CD4/CD8 ratio improved but remained reversed at 0.88.

We do not know if treatment with combination antiretroviral therapy early in the course of primary HIV-1 infection will confer any long-term benefit in terms of preventing the progression of his HIV disease. However, a recent study on the use of zidovudine during primary HIV-1 infection demonstrated reduced frequency of minor opportunistic infections and improved CD4 lymphocyte counts over a 6-month period [9].

Our patient experienced an AIDS-defining event, as defined by the Centers for Disease Control and Prevention, during symptomatic primary HIV-1 infection. However, clinical improvement in his condition occurred only after CMV was cleared from his CNS with specific treatment and the concomitant return of CD4 cell counts to normal. Similar reports of an AIDS-defining event occurring coincident with or shortly after primary HIV-1 infection have been published [24–26]. When such AIDS-defining events occur in a setting of relatively normal CD4 cell counts, they may not have the same prognostic value that they have when they occur during late-stage AIDS. As therapy for acute retroviral syndromes continues to be developed and optimized [9, 27], a word of caution is needed. When a symptom complex is observed that is unusual in severity and duration for primary HIV-1 infection, the possibility of an infecting agent, which may be treatable, must be considered.

Acknowledgments

The authors thank Timothy J. Doyle and John Wilson for excellent nursing care and support and Michael Martino for technical assistance.

References