Cytomegalovirus Polyradiculopathy in Three Japanese Patients with AIDS

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Abstract

Polyradiculopathy (PRP) is a rare but serious neurologic complication of cytomegalovirus (CMV) in patients with acquired immunodeficiency syndrome (AIDS). We herein report three cases of CMV PRP in patients with AIDS. Although providing a prompt diagnosis and initiating anti-CMV therapy may achieve clinical improvements, administering single-drug treatment may result in virologic failure. Therefore, introducing antiretroviral therapy is a key step for improving the treatment outcomes of CMV PRP.

Key words: human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), cytomegalovirus, polyradiculopathy, ganciclovir, foscarnet


Introduction

Cytomegalovirus (CMV) is an important opportunistic pathogen in patients with acquired immunodeficiency syndrome (AIDS) (1), with retinitis and gastrointestinal involvement being the most common manifestations of CMV infection in these patients. The neurological complications of CMV infection are rare but serious, including encephalitis (2), peripheral neuropathy (3) and polyradiculopathy (PRP) (4). Cases of CMV PRP were previously reported primarily before effective antiretroviral therapies (ARTs) became available. However, following the introduction of ART, the incidence of CMV neurological diseases decreased, and there have since been few reports of this condition (5-7). We herein document three cases of CMV PRP in patients with AIDS.

Case Reports

Case 1

A 50-year-old man was referred to our hospital due to gradually progressive dyspnea on exertion, oral candidiasis and positive human immunodeficiency virus (HIV) screening results. No neurological deficits were noted on a physical examination. The HIV-1 RNA level was 1.5×10^4 copies/mL, and the CD4+ cell count was 42/μL. A serological study to detect syphilis showed no active disease, and both Cryptococcal antigens and toxoplasmosis antibodies were negative. Meanwhile, a CMV pp65 antigenemia assay revealed 27 positive cells/slide, and chest computed tomography (CT) of the lungs showed areas of ground-glass opacity, predominantly in the upper lobe. The patient was therefore admitted with a diagnosis of Pneumocystis jirovecii pneumonia, oral candidiasis and HIV infection. Treatment with fluconazole and trimethoprim-sulfamethoxazole was subsequently initiated. However, on day 5, the patient complained of difficulty in urination and consequently received therapy with an alpha blocker. On day 18, he developed bilateral lower leg weakness, and contrast-enhanced (CE) magnetic resonance imaging (MRI) revealed enhancement of the conus medullaris and all nerves of the cauda equina (Fig. 1). A cerebrospinal fluid (CSF) analysis showed a WBC count of 1,813/μL, with 74% polymorphonuclear leukocytes, as well as a protein level of 1,860 mg/dL and glucose level of 29 mg/dL. India ink staining, a Cryptococcus antigen assay and cultures for bacteria, mycobacteria and fungi were nega-
positive, with an HIV-1 RNA level of 4.6×10^4 copies/mL. An HIV screening test was present in the right foot. An HIV screening test was performed on day 2 of admission, showing a normal level of consciousness, and the cranial nerves and upper extremities showed no focal neurological deficits. However, bilateral lower extremity weakness was detected, with a score of 3 on the left and 2+ on the right on an MMT. In addition, the tendon reflexes in both knees and ankles were absent, and a rectal examination revealed a slightly weak sphincter tone. An HIV screening test was also positive, with an HIV-1 RNA level of 1.2×10^4 copies/mL and CD4+ cell count of 34/μL. The results of a test for CMV retinitis. Treatment with ganciclovir (5 mg/kg every 12 hours) and foscarnet (90 mg/kg every 12 hours) was therefore administered. Consequently, the patient’s abnormal sensation in his right foot and difficulty in urination were ameliorated, and his strength in the left lower extremity gradually improved. Thereafter, ART consisting of abacavir, lamivudine and raltegravir was initiated on day 19. A CSF sample obtained on day 22 revealed a CMV DNA level of 4.0×10^4 copies/mL, and, on day 28, the CMV treatment regimen was changed to maintenance oral valganciclovir at a dose of 900 mg daily. The patient’s left lower extremity strength subsequently improved, such that he was able to walk by himself with the help of a cane, and he was discharged on day 33.

Case 2

A 29-year-old man was admitted to our hospital with a one-month history of weakness of the left lower extremity and a tingling sensation in the right foot. On a physical examination, he was found to have a normal level of consciousness, and the cranial nerves and upper extremities showed no focal neurological deficits. However, left lower extremity weakness was apparent, with a score of 4 on a manual muscle test (MMT), and the tendon reflexes in the left knee and ankle were absent. There was no weakness in the right lower extremity, although hyperalgesia upon touch was present in the right foot. An HIV screening test was positive, with an HIV-1 RNA level of 4.6×10^4 copies/mL and CD4+ cell count of 5/μL. The results of a test for the Cryptococcus antigen and serologic assays for syphilis and toxoplasmosis were negative. However, a CMV pp65 antigenemia assay revealed three positive cells/slide, and a CSF analysis showed a WBC count of 291/μL, with 62% of polymorphonuclear leukocytes, as well as a protein level of 269 mg/dL and glucose level of 31 mg/dL. India ink staining, a Cryptococcus antigen assay and cultures for bacteria, mycobacteria and fungi were negative, and lumbar spine MRI performed without contrast showed no abnormalities (Fig. 2a). On day 2, the CSF CMV DNA level was 2.0×10^4 copies/mL. Lumbar spine CE-MRI showed contrast enhancement in the cauda equina predominantly on the left side (Fig. 2b), while an ophthalmologic examination showed CMV retinitis. Treatment with ganciclovir was then administered; however, the patient became comatose and died on day 33.
the Cryptococcus antigen and serologic assays for syphilis and toxoplasmosis were negative, whereas a CMV pp65 antigenemia assay showed 1,182 positive cells/slide. Furthermore, a CSF analysis showed a WBC count of 298/μL, with 63% polymorphonuclear leukocytes, as well as a protein level of 342 mg/dL and glucose level of 42 mg/dL. India ink staining, a Cryptococcus antigen assay and cultures for bacteria, mycobacteria and fungi were all negative. On day 2, the CSF exhibited a CMV DNA level of 1.5×10^8 copies/mL. In addition, a peripheral blood sample showed a CMV DNA level of 6.4×10^7 copies/mL, and an ophthalmologic examination demonstrated CMV retinitis. Therefore, treatment with ganciclovir (5 mg/kg every 12 hours) and foscarnet (90 mg/kg every 12 hours) was started. Lumbar spine CE-MRI consequently showed contrast enhancement in the cauda equina predominantly on the right side (Fig. 3). The patient’s symptoms improved enough within a few days that he was able to elevate both legs completely and stand by himself for one minute; however, his symptoms worsened again on day 9. In addition, a CMV pp65 antigenemia assay performed on day 11 was negative, and, on day 14, the lower extremities showed only muscle contractions, with no visible movement, despite an improvement in the CSF findings (Table 1). Hence, the administration of ART consisting of abacavir/lamivudine and raltegravir was started, with 1 g of methylprednisolone given intravenously on three consecutive days (days 15 to 17). Nevertheless, no improvements were noted, and treatment with ritonavir boosted darunavir was added on day 19. On day 23, the patient exhibited a slight improvement, such that he was partially able to bend his right knee in the horizontal plane and raise his left knee. The CSF CMV DNA level was 25,200 copies/mL on day 27 (Table 1), and the dose of ganciclovir was discontinued on day 29 due to myelosuppression. However, the patient improved enough to stand with assistance on day 33 and, two weeks later, was able to walk by himself with the help of a cane. The dose of foscarnet was then decreased to a maintenance dose of 90 mg/kg once daily on day 47. Soon thereafter, the patient noticed fatigue and anorexia, and a CSF examination performed on day 50 showed an elevated CMV DNA level of 1.4×10^6 copies/mL, with a peripheral blood CMV DNA level of 470 copies/mL. The treatment regimen was intensified to the induction doses of ganciclovir (5 mg/kg every 12 hours) and foscarnet (90 mg/kg every 12 hours), after which the patient’s symptoms improved. The CSF CMV DNA level was 2.9×10^5 copies/mL on day 56 and 5.9×10^4 copies/mL on day 63. After two weeks of induction therapy, a regimen consisting of valganciclovir at a dose of 900 mg once daily was started; however, a CMV DNA profile showed no known mutations related to resistance to ganciclovir or foscarnet. The patient was subsequently discharged on day 72, at which time he was capable of walking by himself with the help of a cane. The dose of raltegravir was stopped on the day of discharge, while the therapy with abacavir/lamivudine and ritonavir boosted darunavir was continued.

**Discussion**

Central nervous system (CNS) diseases caused by CMV have a very poor prognosis despite the availability of anti-CMV therapy. Anders et al. reviewed 103 cases of CMV PRP treated between 1984 and 1997, in the pre-ART era (4), and found a mean survival time for the untreated patients and those treated with ganciclovir of 5.4 and 14.6 weeks, respectively. Since the introduction of ART, there has been only one case series describing the characteristics and outcomes of patients with CMV PRP (7), with several single case reports (8-10). In that series, Silva et al. reported 13 cases of neurologic CMV complications in patients with AIDS, including seven cases of CMV RPR (7). The authors noted that four of the seven patients were discharged, while three died. In the present study, the patients in Cases 2 and 3 showed a significant clinical response and were ultimately

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**Figure 3.** Lumbar spine MRI performed in Case 3. A gadolinium-enhanced T-1 sequence showed contrast enhancement in the cauda equina predominantly on the right side (arrow).

| Table 1. The Results of Cerebrospinal Fluid Analysis in Case 3 |
|----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                      | Day 2 | Day 13 | Day 20 | Day 27 | Day 36 | Day 43 | Day 50 | Day 56 | Day 63 |
| Leukocytes (μL)      | 298   | 13    | 5     | 11    | 23    | 15    | 25    | 24    | 8     |
| Protein (mg/dL)      | 342   | 204   | 41    | 148   | 189   | 154   | 126   | 147   | 111   |
| CMV-PCR (copies/mL)  | 1.5×10^5 | 4.7×10^5 | 1.8×10^5 | 2.5×10^5 | 8.9×10^4 | 1.8×10^5 | 1.4×10^5 | 2.9×10^4 | 5.9×10^4 |

CMV: cytomegalovirus
PCR: polymerase chain reaction
The details of our three cases are summarized in Table 2. The use of ART has been reported to improve the outcomes of CNS herpes viruses infection in patients with HIV (11). It is therefore reasonable to consider that the outcomes of CMV PRP are better in the ART era than in the pre-ART era.

The delay in initiating anti-CMV therapy may have led to the treatment failure observed in Case 1. Silva et al. also reported that the median time from admission to diagnosis was significantly longer in their patients with CMV neurologic disease who died (7). Other conditions reported to cause manifestations similar to those of CMV PRP include herpes simplex virus 2 infection (12), varicella-zoster virus infection (13), toxoplasmosis (14), syphilis (15), malignant lymphoma (16) and diffuse infiltrative lymphocytosis syndrome (17). Silva et al. reported that 54% of patients with neurologic diseases caused by CMV present with extraneurral CMV disease, including a rate of retinitis of 31% (7). Two of our three patients displayed CMV retinitis. The detection of extraneural CMV disease is helpful for diagnosing neural involvement of CMV.

The characteristic features of the CSF in affected patients include polymorphonuclear pleocytosis, an elevated protein level and a decreased glucose level (18). These features resemble those of bacterial meningitis. The patient in Case 1 in this study was first treated for bacterial meningitis, resulting in a diagnostic delay. pp65 antigenemia assays have a limited role in diagnosing CMV PRP, and Silva et al. reported that 37.5% of patients with CMV neurologic diseases are negative for pp65 antigenemia (7). In our cases, the pp65 antigenemia assay results did not correlate with the CMV viral load in the CSF (Table 2). The diagnosis of CMV is usually made based on the detection of CMV DNA in the CSF on PCR (19).

The most commonly recommended treatment agents in cases of CMV are ganciclovir, foscarnet or a combination of both (20-23). Anduze-Faris et al. reported that, in their study, ganciclovir-foscarnet combination therapy resulted in a clinical improvement or stabilization in 74% of cases (21). Guidelines in the US include a soft recommendation for the administration of combination therapy according to expert opinion (24). In the present study, the patients in Cases 2 and 3 were promptly treated with a combination of ganciclovir and foscarnet, and both were able to walk again.

### Table 2. Summary of Main Clinical and Laboratory Characteristics of the Three Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Sex</td>
<td>50/male</td>
<td>29/male</td>
<td>54/male</td>
</tr>
<tr>
<td>CD4+ cell count (cells/µL)</td>
<td>42</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>HIV-1 RNA (copies/mL)</td>
<td>1.5×10^4</td>
<td>4.6×10^4</td>
<td>1.2×10^6</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td>Urinary retention Bilateral lower extremity weakness</td>
<td>Urinary retention Left lower extremity weakness Right lower extremity hyperalgia</td>
<td>Urinary retention Bilateral lower extremity weakness</td>
</tr>
<tr>
<td>Extra-neural CMV disease</td>
<td>None</td>
<td>Retinitis</td>
<td>Retinitis</td>
</tr>
<tr>
<td>pp65 antigen (cells/slide)</td>
<td>27</td>
<td>3</td>
<td>1,182</td>
</tr>
<tr>
<td>CSF WBC count (µL)</td>
<td>1,813</td>
<td>291</td>
<td>298</td>
</tr>
<tr>
<td>% of PMN of WBCs</td>
<td>74</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>CSF protein level (mg/dL)</td>
<td>1,860</td>
<td>269</td>
<td>342</td>
</tr>
<tr>
<td>CSF glucose level (mg/dL)</td>
<td>29</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>CSF CMV DNA (copies/mL)</td>
<td>&gt;1.0×10^8</td>
<td>2.0×10^9</td>
<td>1.5×10^8</td>
</tr>
<tr>
<td>Time from admission to diagnosis (days)</td>
<td>28</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treatment</td>
<td>Ganciclovir</td>
<td>Ganciclovir + Foscarnet</td>
<td>Ganciclovir + Foscarnet</td>
</tr>
<tr>
<td>Outcome</td>
<td>Died on day 33</td>
<td>Alive</td>
<td>Alive</td>
</tr>
</tbody>
</table>

HIV: human immunodeficiency virus, CMV: cytomegalovirus, CSF: cerebrospinal fluid, WBC: white blood cell, PMN: polymorphonuclear
walk home by themselves upon discharge. However, combination therapy may induce severe side effects during induction therapy, leading to drug discontinuation in approximately one-third of patients (21). Both of our patients who received combination therapy suffered only mild myelosuppression.

CSF CMV DNA PCR is also reported to be useful for monitoring the response to therapy in patients with CMV CNS disease (25). This is the first report to describe the findings of CSF CMV DNA PCR in detail. The patient in Case 3 showed virological failure under treatment with foscarnet monotherapy, in which the viral load in the blood was suppressed, while the viral load in the CSF showed marked elevation. We subsequently restarted the administration of the combination regimen, and the CSF viral load rapidly decreased. In addition, the CMV in the CSF showed no resistance to ganciclovir or foscarnet. The patient’s extremely high initial CMV viral load may have induced the virologic failure associated with the single-drug regimen. In the current cases, the CSF CMV DNA levels remained relatively high at the time of discharge, despite various clinical improvements. Cinque et al. reported that, in their study, a remarkable proportion of patients with CMV encephalitis showed detectable CSF CMV DNA after receiving a three-week treatment regimen (25). Therefore, further studies with large sample sizes are needed to determine the appropriate degree of CSF CMV DNA reduction sufficient to achieve a clinical improvement.

We administered high-dose steroid therapy in Case 3 because the patient’s lower extremity weakness progressed despite a reduction in the CMV viral load. Previous reports have shown the possible efficacy of high-dose steroid therapy in immunocompetent patients with transverse myelitis, including a case of CMV infection (26-28), although one study failed to demonstrate any benefits (29). Our patient exhibited no improvements after receiving high-dose steroid therapy. The administration of steroids in patients with HIV may induce severe immunosuppression; therefore, we did not continue the steroid maintenance therapy in this case.

There are no established data regarding when to initiate ART in patients with neurological CMV disease. In Case 3, we administered ART after the patient had showed no improvements with combination anti-CMV therapy for two weeks. HIV infection itself can cause lower extremity weakness (30), and a persistent severely low CD4+ cell count may result in the onset of other opportunistic infections. In the present case, the patient’s HIV-1 RNA level decreased quickly without signs of inflammatory reconstitution syndrome after starting ART.

In conclusion, we herein reported three cases of CMV PRP in patients with AIDS in whom the prompt initiation of anti-CMV therapy led to reductions in the CMV viral load with an associated functional recovery. Introducing ART is important for improving the outcomes of such patients, although the optimal timing for initiating this treatment is unclear.

The authors state that they have no Conflict of Interest (COI).

References

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