Progressive multifocal leukoencephalopathy (PML) is an opportunistic demyelinating infection caused by the ubiquitous, usually nonpathogenic JC papovavirus. The virus infects and destroys oligodendrocytes, the myelin-producing cells of the central nervous system (CNS), thereby causing patchy areas of demyelination in the cerebral white matter. It is exclusively a disease of immunosuppressed individuals. This article discusses a case of PML as an initial manifestation of AIDS in a 48-year-old man. The epidemiology, pathogenicity, and diagnostic evaluation of PML are discussed, and recent research into the effectiveness of antiretroviral therapy in treating PML in patients with AIDS is reviewed.

CASE PRESENTATION
Patient Presentation
A 48-year-old left-handed man presented with a 4-month history of a progressive neurologic syndrome manifesting as hemiparesis and cognitive, visual, and language difficulties. The patient lived outside of the United States and his native language was Spanish; he spoke English as a second language. His initial evaluation at our institution and all subsequent physical and neurologic evaluations were conducted with one of his treating physicians acting as an interpreter.

Four months prior to presentation, the patient noted decreased vision and mild pain in his right eye. Three days later, he noted onset of right hand clumsiness, unsteady gait, forgetfulness, and mild headache. At that time, he was on a business trip in South America and became unable to conduct his usual business activities. Evaluation with brain magnetic resonance imaging (MRI) when he returned home demonstrated a lesion in the left cerebral hemisphere of undetermined nature. No further investigation or treatment was recommended.

One month prior to presentation, he noted the onset of an inability to express himself verbally. He became unable to sign his own checks. He also developed a tremor in his right hand. The symptoms were progressive, and he was referred to our institution for further evaluation.

The patient was the owner of a corporate travel company and frequently traveled throughout Europe, Asia, and South America. He had no history of any prior medical illness and did not experience any prodromal or viral-like illness prior to the onset of his symptoms. He consumed an average of 2 to 3 ounces of alcohol daily, and he stopped smoking 12 years previously. He denied any history of known HIV infection, promiscuous bisexual or homosexual relationship, and exposure to blood or blood products.

Physical Examination
The patient was afebrile, weighed 75 kg, and was 174 cm tall. Blood pressure was 120/80 mm Hg. Results of the general physical examination were normal.

On neurologic examination, he was alert, attentive, and oriented to name, place, and time. He followed 1-step commands well but had marked difficulty with multistep commands. His speech was telegraphic, but comprehension appeared intact. Object naming and writing of full sentences were severely impaired. Visual acuity was 20/20, –1 bilaterally. He had a right homonymous hemianopsia and right-sided weakness in an upper motor neuron distribution. Muscle tone was increased in the right arm and leg, and he had a right-sided hyperreflexia. He had bilateral ankle clonus and a right extensor plantar response. He had a wide-based, right circumductive gait, with the right upper extremity flexed at the elbow and held across his chest. He also had nonpurposeful and nonrhythmic movements of the right arm superimposed on a low-amplitude rhythmic postural and kinetic tremor.

Laboratory Evaluation
Leukocyte and platelet counts, hemoglobin and blood glucose levels, and results of liver, kidney, and...
thyroid function tests were within normal limits. Serology screens for hepatitis A, B, and C viruses were negative, and results of urinalysis were within normal limits. Cerebrospinal fluid (CSF) serologies for cryptococcus, toxoplasma, cytomegalovirus, and syphilis were negative. Polymerase chain reaction (PCR) for herpes simplex virus was negative. Acid-fast bacilli stain was negative, and fungal cultures showed no growth. Abnormal laboratory results are shown in Table 1.

Radiographic Evaluation

Contrast-enhanced brain MRIs with fluid-attenuated inversion recovery (FLAIR) and T2-weighted techniques demonstrated large confluent areas of hyperintense signal involving the white matter of the left frontal, temporal, parietal, and occipital lobes with extension to subcortical U-fibers (white-matter tracts that run from subcortical gray matter to subgyral cortex). There was extensive involvement of the splenium of the corpus callosum with minimal mass effect on the occipital horn of the left lateral ventricle. The white-matter lesion crossed the midline to involve the contralateral deep white matter of the occipitoparietal lobe. No significant enhancement or midline mass effect was present (Figure 1).

Compared to the study of 1 month earlier, significant progression of the lesion was noted. At the 4-week posttreatment evaluation, the patient had improved but had persistent word-finding difficulties and telegraphic speech. He made paraphasic errors on reading. His right hemiparesis was unchanged. Venlafaxine 37.5 mg daily was started for newly diagnosed secondary depression with anxiety. His CD4+ cell count was stable at 180 cells/mm³. HIV-1 RNA viral load decreased to 7,806 copies/mL. Evaluation 4 months posttreatment revealed continued improvement in language deficit with only mild telegraphic speech. His right hemiparesis had significantly improved from baseline, and he was able to ambulate without assistance. HIV-1 RNA viral load decreased further, to 574 copies/mL, and his CD4+ cell count increased to 194 cells/mm³. Repeated brain MRI demonstrated decreased mass effect on the occipital horn of the left lateral ventricle. The right cerebral white-matter lesion improved, but the left occipitoparietal white-matter lesion remained essentially unchanged (Figure 2). In addition, new areas of increased signal intensity involving the brainstem corticospinal tracts had developed. This change was thought to be most consistent with wallerian degeneration, although extension of the primary disease could not be excluded. Continued follow-up every 3 to 4 months was planned.

DISCUSSION

PML was first identified in 1958 as a rare complication of chronic lymphocytic leukemia and Hodgkin’s disease. Padgett and colleagues isolated the causative JC virus in 1971. Although PML is relatively uncommon, the AIDS epidemic has resulted in a remarkable increase in its frequency, thus enabling more detailed analysis of all aspects of this previously rare disorder.

Epidemiology

Seroepidemiologic studies show that infection with the JC virus is common and usually occurs during childhood. The JC virus has been shown to persist in the kidneys and is shed in the urine. More than 80% of the human adult population is seropositive for JC virus–specific antibodies. Despite this high prevalence of infection, JC virus–induced disease is rare, occurring almost exclusively in immunosuppressed individuals. PML has been estimated to affect approximately 4% of

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**Table 1. Abnormal Laboratory Results of Case Patient**

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV test (ELISA and Western blot assay)</td>
<td>Positive</td>
</tr>
<tr>
<td>CD4+ lymphocyte count</td>
<td>184 cells/mm³ (expected: 401–1,532 cells/mm³)</td>
</tr>
<tr>
<td>CD4+/CD8+ cell ratio</td>
<td>0.16 (expected: &gt;1)</td>
</tr>
<tr>
<td>HIV-1 RNA level</td>
<td>32,204 copies/mL (expected: 0 copies/mL)</td>
</tr>
<tr>
<td>CSF cell count</td>
<td>7 cells/mm³ (expected: 0–5/mm³)</td>
</tr>
<tr>
<td>CSF protein level</td>
<td>98 mg/dL (expected: &lt;45 mg/dL)</td>
</tr>
<tr>
<td>CSF oligoclonal bands</td>
<td>2 (expected: 0–1)</td>
</tr>
<tr>
<td>CSF synthesis rate</td>
<td>46.87 mg/24 hr (expected: 0–12 mg/24 hr)</td>
</tr>
<tr>
<td>CSF PCR for JC virus</td>
<td>Positive</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction.

and lamivudine) 1 tablet twice daily and nelfinavir 250 mg 5 tablets twice daily. Prophylaxis for *Pneumocystis carinii* pneumonia (trimethoprim/sulfamethoxazole) was also initiated. He received vaccines for influenza, pneumococcus, and hepatitis A and B viruses, and a tetanus booster shot. Physical and speech therapy was instituted and continued on an outpatient basis.

The patient was started on highly active antiretroviral therapy (HAART) consisting of Combivir (zidovudine and lamivudine) 1 tablet twice daily and nelfinavir 250 mg 5 tablets twice daily. Prophylaxis for *Pneumocystis carinii* pneumonia (trimethoprim/sulfamethoxazole) was also initiated. He received vaccines for influenza, pneumococcus, and hepatitis A and B viruses, and a tetanus booster shot. Physical and speech therapy was instituted and continued on an outpatient basis.

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Epidemiology

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patients with AIDS. Survival after the diagnosis of leukoencephalopathy in untreated patients and in patients treated with a single antiretroviral agent averages 4 months. Approximately 7% of affected patients follow a relatively benign course, with survival of 1 year or more. Remission and partial recovery in patients treated with HAART may occur. Prolonged survival has been reported in patients with PML as the AIDS-defining illness and in those with high CD4+ cell counts (>90/mm³) at presentation.

**Pathogenicity**

The neurologic signs and symptoms of PML result from the viral destruction of myelin-producing oligodendrocytes in the CNS. The main pathologic features of PML include multiple foci of myelin and oligodendroglial cell loss, hyperchromatic enlarged oligodendroglial nuclei, and bizarre astrocytes with enlarged multilobulated nuclei. The widespread and multifocal distribution of the demyelinating lesion suggest a hematogenous viral spread to the CNS.

**Diagnosis and Differential Diagnosis**

The classic triad of PML includes visual deficits, upper motor neuron weakness, and altered mental state. Language and speech dysfunction, extrapyramidal syndromes, cerebellar disorders, sensory deficits, headaches, and seizures may also occur. The latter symptoms may occur as the initial manifestations of PML when it presents as an AIDS-defining illness, but they are more frequently encountered in patients with PML in whom AIDS was previously diagnosed.

The neuroimaging characteristics of PML are decreased attenuation on computed tomographic scans and hyperintense signal on T2-weighted MRI. The lesions most often involve periventricular and subcortical white matter of the occipitoparietal or frontal lobes.
Occasionally, the posterior fossa is involved. Rarely do the lesions show contrast enhancement or produce mass effect. However, a single case report of mass effect associated with PML does exist. Other disorders that may mimic PML include cytomegalovirus and Epstein-Barr virus infections, toxoplasma encephalitis, CNS lymphoma, and encephalitis caused by HIV infection. A definitive diagnosis requires evaluation of brain tissue, but recent studies indicate that the presence of JC virus in CSF can be identified by PCR with high specificity and sensitivity. In a prospective cohort study of AIDS patients with focal brain lesions, Antinori and colleagues found that absence of mass effect on neuroimaging studies and a positive CSF viral DNA test for the JC virus yielded a 0.99 probability of making a diagnosis of PML. They concluded that a positive result of JC virus DNA testing of the CSF may obviate the need for brain biopsy in a patient with typical focal brain lesions without mass effect. Clinical and neurodiagnostic characteristics alone may not effectively discriminate between toxoplasma encephalitis and CNS lymphoma in seronegative patients or patients with a focal brain lesion with mass effect who are undergoing antitoxoplasma prophylactic treatment. Brain biopsy remains a necessary procedure in these patients.

**Treatment**

AIDS-associated PML is a rapidly progressive and fatal disease. In a study of 154 patients with HIV-associated PML, the median survival was 6 months, and only 3.9% of the patients survived beyond 12 months. Prolonged survival and recovery of neurologic deficits consequent to PML have been seen on rare occasions in association with underlying immunosuppressive conditions other than AIDS, and in patients with AIDS who were treated with triple HAART that included a protease inhibitor (Table 2). Currently there is no proven therapy for AIDS-related PML. A randomized, multicenter, open-label study recently evaluated the effectiveness of antiretroviral therapy (zidovudine and didanosine or zidovudine and zalcitabine) alone, antiretroviral therapy plus intravenous cytarabine (a cell-cycle phase-specific antineoplastic agent), or antiretroviral therapy plus intrathecal cytarabine in 57 patients with HIV infection and biopsy-proven PML. No significant difference in survival among the groups was found. There are case reports of improved immunologic and neurologic status of AIDS patients with PML treated with HAART that included a protease inhibitor. However, a case control study found no significant benefit of HAART over cytarabine therapy. Although promising, HAART versus conventional therapy has not been studied in a randomized, controlled clinical trial of subjects with AIDS-associated PML. The mechanism by which improvements occur in patients with PML treated with HAART is not known. Reduction of the viral load with improvement of immune function has been postulated.

**SUMMARY**

PML is a fatal demyelinating CNS infectious disease that exclusively affects immunocompromised individuals. JC virus, the etiologic agent for PML, is ubiquitous in the general population but rarely causes disease in immunocompetent hosts. PML is most commonly seen in patients with a previous diagnosis of AIDS, but it can be the presenting symptom of AIDS. Diagnosis can be
confidently made on a clinicovirologic basis, but confirmation requires histologic examination of brain tissue. Currently, there is no proven effective therapy for PML, but HAART holds a promising future for the treatment of this rare but fatal disease.

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**REFERENCES**


