A 31-Year-Old Man Who Presents with Speech Abnormalities

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CASE REPORT

A 31-year-old man with advanced human immunodeficiency virus (HIV) infection presented to the emergency department with “altered mental status” (AMS) for two months and blurry vision for one day. The patient and his family began to notice that he would “stumble over words” while he spoke. Three weeks prior to presentation, he started calling people by the wrong name, and eventually, was unable to answer questions, properly identify objects or converse normally. Per family, he understood what was asked but could not express a proper response. On the morning of his admission, the patient complained that he could not see his girlfriend clearly, only her silhouette, prompting her to bring him to the emergency department. Review of systems was otherwise unremarkable, including no weakness or changes in gait or sensation.

The patient was diagnosed with HIV seven years prior. He had only visited his HIV physician three times since 2007 and had never taken combination antiretroviral therapy (cART). Labs from clinic 40 days prior to presentation showed a total CD4 count of 6 cells/mm³ (228-2290 cells/mm³), CD4 percentage of 2.4% (37-63%) and a viral load of 121,738 copies/ml. The plan at that time was to begin cART therapy once his HIV genotype was obtained. The patient had a past medical history of oropharyngeal candidiasis, pneumonia and herpes zoster. His medications at the time of presentation included azithromycin and trimethoprim/sulfamethoxazole (TMP/SMX) for prophylaxis against opportunistic infections. The patient continued to smoke, but denied any alcohol or illicit drug use. He was living at home with his girlfriend and had two daughters, one of whom was also HIV-positive.

On presentation, vital signs included a temperature of 98°F, heart rate of 88 beats/min, respiratory rate of 16 breaths/min, blood pressure of 113/73 mmHg and an O₂ saturation of 100 percent on room air. He weighed 148 pounds with a body mass index of 21. The patient was in no acute distress and oriented to person, but was unable to accurately identify the time or place, stating “I know what the answer is, but I can’t say it.” A more thorough neurologic assessment was consistent with a Wernicke’s type aphasia, showing intact comprehension but difficulty following commands, fluent speech with highly disorganized syntax, and the inability to name objects or repeat phrases. Visual fields were intact without gross visual deficiencies. The remainder of the physical exam revealed oropharyngeal candidiasis. Laboratory studies were within normal limits except for a low white blood cell (WBC) count of 4,000x10³/µL (4.5-11x10³/µL), with 80% neutrophils, 9% lymphs, 0% bands, 5% eosinophils and 6% monocytes. A computed tomography (CT) scan of the head without contrast showed development of a predominantly left-sided periventricular and subcortical low density process suggestive of a demyelinating process without significant mass effect or appreciable volume loss (Figure 1); this was significantly changed from a head CT that was reported as normal seven months earlier. Based upon initial imaging and presenting symptoms, a presumptive diagnosis of progressive multifocal leukoencephalopathy (PML) was entertained and the patient was admitted for additional testing.

Neurology and ophthalmology were consulted for the patient’s neurologic deficits and blurry vision, respectively. MRI with and without gadolinium IV contrast enhancement showed extensive abnormal T2 hyperintensity within the white matter of the left cerebral hemisphere, most prominently within the left parietal and temporal lobes, including extensive involvement of the subcortical U-fibers (Figures 2 and 3). Figure 3A shows involvement of the posterior portion (splenium) of the corpus callosum.
Additionally, there was a notable lack of enhancement in these abnormal regions on post-contrast T1 weighted series (Figure 4). Finally, as an indication of both the severity and destructive capacity of the infectious process, pre-contrast and post-contrast MRI images demonstrated cavitary changes (Figures 5A and 5B, respectively) within the subcortical white matter of the left cerebral hemisphere (white arrows). Neurology agreed that PML was the likely diagnosis and ophthalmology determined that there were no signs of ocular involvement in the patient's visual impairment. A lumbar puncture showed mildly elevated protein in the cerebrospinal fluid (CSF) with a normal glucose and WBC count. CSF cryptococcal antigen and Epstein-Barr virus polymerase chain reaction (PCR) were negative, but the CSF John Cunningham (JC) virus PCR assay was positive. The combination of the clinical presentation, MRI findings, and positive JC virus PCR results confirmed the diagnosis of PML. The patient was started on HIV genotype-directed cART.

**EPIDEMIOLOGY AND PATHOPHYSIOLOGY**

Progressive multifocal leukoencephalopathy is primarily a disease of immunosuppressed individuals with HIV-infected individuals currently accounting for 80 percent of all cases.\textsuperscript{1,2} The incidence of PML has declined from 3.3 cases/1000 patient-years at risk (1995 to 1996) to 1.3 cases/1000 patient-years at risk (2000 to 2006) following the widespread use of cART.\textsuperscript{3} The first recorded case of the demyelination disease termed PML was reported in a patient with chronic lymphocytic leukemia (CLL) and Hodgkin’s lymphoma in 1958 with a potential viral etiology described the following year.\textsuperscript{4,5} Concurrent with the rise in HIV infections, previously rare reports of PML increased, occurring in 3 to 5 percent of all HIV-positive patients.\textsuperscript{6,7} The etiology behind the higher incidence of PML in HIV-infected patients versus other causes of immunosuppression remains unclear. Possible mechanisms include HIV’s effect on immune cell trafficking or permeability of the blood brain barrier; intrinsic damage caused by HIV and possible synergism between HIV and JC virus in co-infected cells have also been proposed.\textsuperscript{2,6,8} Furthermore, CD4+ T-lymphocytopenia has been associated with an increased incidence of PML, lending support to the notion that a reduction in CD4+ T cells leads to a lack of immunomodulation of JC virus suppression.\textsuperscript{9,10} Other conditions that can cause a profound immunosuppression associated with PML include hepatic cirrhosis, renal failure, leukemia, lymphoma and transplant patients. More recently, PML has been reported in patients being treated with immunosuppressive drugs, including efalizumab (withdrawn from the market), infliximab, mycophenolate mofetil, rituximab, and most notably, natalizumab.\textsuperscript{6,8} Studies show that...
the incidence of immunosuppressive therapy-associated PML increases as treatment length progresses.6

While cART is the primary means by which to treat HIV-positive individuals with PML, immune reconstitution inflammatory syndrome (IRIS) associated with the initiation of antiretrovirals can be linked with worsening or even life-threatening changes to the course of PML.8,11 As such, previously undiagnosed PML may be seen during the early stages of HIV therapy with paradoxical immune improvement and cognitive deterioration seen in this subset of patients. IRIS is not unique to PML, but an important consideration when commencing cART. The mechanism behind IRIS is thought to result from resumption of immune surveillance in the CNS, thus causing the initial worsening of neurological symptoms. Enhanced CD8+ -mediated inflammatory changes observed in IRIS can often be identified by gadolinium enhancement on MRI.12 In fact, clinical diagnosis is based on MRI and an increase of the CD8+ and CD4+ T cell counts (>200 cells/mm³).6 Among patients with HIV, predictors for the development of IRIS include patients that are cART naïve, patients with profoundly low CD4+ lymphocyte counts (<50 cells/mm³), a rapid decrease in HIV load, and the presence of active or subclinical opportunistic infections.11 Therefore, careful patient monitoring is imperative at the start of cART.

Figure 3: Axial T2 FLAIR MR images demonstrating multifocal, bilateral, and asymmetric abnormal hyperintensity within the subcortical and deep white matter. Axial image (A) demonstrates involvement of the periventricular white matter and corpus callosum. Axial image (B) demonstrates involvement of the left cerebral peduncle (white arrow) as well as the white matter of the left temporal and occipital lobes.

Approximately 60-80 percent of the human population harbors antibodies to JC virus, and at any given time, one-fifth of the population sheds JC virus in their urine.7,13 Interestingly, JC virus, a member of the Polyomaviridae family, is fairly isolated to humans, and due to its ubiquity within individual populations across the globe, specific viral subtypes have been used to map population movements.6 Asymptomatic infection typically occurs during childhood, and though the exact mechanism of transmission is unknown, it is suspected to be via a fecal-oral route.14 Once inside its host, the virus predominantly transfects renal tubular epithelial cells within the kidney and is detectable in urine 3 to 5 days post infection.6,15,16 The migration of JC virus to the CNS is not well understood and numerous studies have failed to delineate the mechanism, though the proposed route is likely hematogenous, owing to the multifocal lesions observed on imaging and postmortem evaluation. As such, it appears that PML is the result of reactivation of latent JC virus previously suppressed by a healthy immune system. Once JC virus translocates into oligodendrocytes within the CNS, specifically the white matter of the brain, it causes cellular lysis and the resultant local spread, ultimately triggering permanent neuronal demyelination and impaired electrical propagation.6
**Figure 4:** Axial T1-weighted contrast-enhanced MR images (A) and (B) demonstrate the typical pattern of non-enhancement within the affected white matter of the left cerebral hemisphere (white arrows).

**Figure 5:** Axial T1-weighted non-contrast MR image (A) and axial T2 weighted MR image (B) demonstrate cavitory changes within the white matter of the left cerebral hemisphere (white arrows).
CLINICAL PRESENTATION

A majority of HIV-associated PML cases involve patients with CD4+ T-cell counts <200 cells/mm³, with the symptoms of PML occurring insidiously and often going unnoticed during the disease onset.6,11,15 Thus, significant cognitive and/or motor impairment is typically observed prior to patient presentation to a physician and can be easily mistaken as a stroke. Once observed, cognitive deterioration can progress rapidly over days to weeks if left untreated. Though PML can present in any region of the brain, including the cerebral hemispheres, its predilection for more posterior sites, including the brain stem, cerebellum and occipital lobes, account for the more common clinical symptoms observed in PML.6,11 In patients with HIV-associated PML, the most common presenting complaints include weakness (42%), speech abnormalities (40%), cognitive abnormalities (36%), gait abnormalities (29%), sensory loss (19%), and visual impairment (19%), followed by seizures, diplopia, and uncoordinated limb movements.6,11 Thus, predictably, the most common symptoms found on initial physical examination are weakness (54%), followed by gait abnormalities (20%), cognitive abnormalities (20%), dysarthria (24%), aphasia (19%), sensory loss (19%), visual impairment (17%), and oculomotor palsy (6%), though a wide variety of other manifestations exist.6,11 These symptoms help to differentiate PML from HIV encephalopathy or other HIV-associated neurocognitive disorders, though they should be included in the preliminary differential diagnosis. As PML progresses, seizures can be often observed, occurring in up to 18 percent of affected patients.17 The disease course and prognosis of PML are generally poor, with nearly universal mortality in untreated, HIV-infected individuals within 2 to 4 months, and within 9 months in non-HIV-positive patients.18,19 With the institution of cART, PML survival rates have improved with a median life expectancy of about 12 to 24 months.11,20 Unfortunately, those who do survive are often left with severe neurologic morbidities and a reduced quality of life. Early recognition and treatment is paramount to improved outcomes.

DIAGNOSIS AND TREATMENT

Diagnostic confirmation of PML requires positive detection of JC virus DNA within the CNS and characteristic CT or MRI imaging.21 While JC virus antibody testing can be done in plasma, it is of little diagnostic value since use of immunomodulating therapies can cause a false negative result. Plasma viral loads do not seem to correlate to disease incidence or severity, and patients can have PML without the presence of viremia.6,11 Thus, CSF studies are more conclusive, especially considering that PCR detection of JC virus DNA is almost 100 percent specific with no cross-reaction to DNA regions of other viruses.6 Furthermore, some PCR assays can detect JC virus levels as low as 10 copies/ml.6,21 Imaging studies are also of diagnostic importance. Computed tomography typically shows patchy and/or diffuse hypodense regions within the white matter.22 MRI is the more sensitive modality and imaging typically includes contrast enhanced T1 hypointense or T2 FLAIR hyperintense signals in the subcortical white matter.2,12,23 While these tests are considered adequate for the diagnosis of PML and the initiation of subsequent treatment, the gold standard remains tissue histopathology.2,6,15,21 Histologically, demyelinated plaques are observed surrounded by oligodendrocytes containing prominent intranuclear eosinophilic inclusion bodies, as well as bizarre, hyperchromatic, multinucleated, and sometimes multineucleated astrocytes.15,21,23 These lesions may contain foamy myelin-filled macrophages with or without axonal sparing. As the disease progresses, microscopic areas of demyelination within these plaques can coalesce to become macroscopic cystic cavities or plaque lesions with a dusky grey-brown appearance and areas of tissue softening on sagittal sectioning of autopsy brain specimens.15,23

In patients diagnosed with HIV-associated PML, the sole treatment option is combination antiretroviral drug regimens designed to improve immunological response. With the introduction of cART, both morbidity and mortality have improved by decreasing disease severity and increasing length of survival. Regardless, PML maintains the worst prognosis of any cerebral AIDS-related disorder, with those having more advanced immunosuppression being most susceptible and negatively affected by the disorder.11,20 Though the possibility of IRIS-induced PML deterioration can occur, AIDS patients with PML who were antiretroviral-naive at the time of diagnosis appear to have better survival than treatment-experienced patients.1,24 This is likely due to the fact that PML development presenting in the face of appropriate cART denotes a profoundly immunosuppressed state or a severely advanced HIV status.24 Survival also correlates with reduced JC virus load in the CSF and improved CD4+ lymphocyte counts (CD4+ counts >100 cells/mm³).11,25,26

Currently, no specific combination of antiretroviral drugs confers greater protection or resolution against PML. Therefore, the specific combination depends primarily upon the HIV genotype, antiretroviral sensitivities, and the individual patient response. Upon the diagnosis of PML, CART should be started immediately with appropriate monitoring according to the latest guidelines on follow-up CD4 counts and HIV viral loads.27 In HIV-positive PML patients, CART initiation resulted in a nearly 50 percent cessation of PML disease progression, and though neurological deficits generally persisted, some patients reported clinical improvement.21 Retrospective studies have shown that survival improved from a mean of six months in pre-cART years to 1 to 3 years, though roughly half of surviving patients experienced moderate-to-severe disability.11,20,25 Other treatment modalities have been proposed and, in some cases, trialed, including cidofovir and cidofovir, but with little to no success.25,28 The use of serotonergic 5-HT2a receptor blockers, including the anti-psychotics olanzapine, zisprasidone and risperidone, have been considered since JC virus glial cell entry may occur via this receptor, but clinical studies have...
Thus far not been conducted. Consequently, life-long cART remains the mainstay in PML therapy.

In conclusion, HIV-associated PML, a consequence of JC virus reactivation in severely immunocompromised patients, is a demyelinating disease associated with debilitating cognitive and functional morbidity and high mortality. Current diagnostic criteria include clinical presentation, detection of JC virus within the CSF and typical brain CT or MRI findings showing changes in the subcortical white matter. Initiation of cART is recommended, resulting in improved morbidity and survival. As with most HIV-associated comorbidities, minimizing viral replication and immune suppression remains the most effective approach to reducing the debilitating and often fatal effects of progressive multifocal leukoencephalopathy.

REFERENCES

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