Progressive Multifocal Leukoencephalopathy/JC Virus Infection

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Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the human polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] JCV has a worldwide distribution, and 20% to 70% of people exhibit serologic evidence of exposure by their late teens or as adults.[3-7] Primary JCV infection usually occurs asymptomatically in childhood resulting in a chronic carrier state in most individuals. Viral DNA is detected in the urine of 20% to 30% of healthy adults.[4,8-12]

PML is a rare manifestation of JCV reactivation and characteristically manifests as a complication of HIV-1 infection and other immunocompromising diseases or therapies.[13-16] In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab[17] and efalizumab.[18] Concern has been raised about a possible increased risk of PML in persons with HIV (PWH) treated with rituximab for non-Hodgkin lymphoma,[19,20] but PML has not been documented in that setting. PML can occur during chronic immunosuppression after organ transplantation and often has a poor prognosis.[21]

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS[22-24] and was almost invariably fatal; spontaneous remissions were rare.[25] With the widespread use of ART, incidence of PML decreased substantially,[26,27] and mortality in PWH who develop the disease has declined.[28-30] Although most CNS opportunistic infections are effectively prevented when CD4 T lymphocyte (CD4) cell counts are maintained above 100 to 200 cells/mm^3, PML still occurs occasionally in patients treated with ART.[2,31,32] PML also can develop in the setting of immune reconstitution after ART initiation, which is discussed below.[2,30,33]

Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Although some regions seem to be more favored, any region of the CNS can be involved, including the occipital lobes (hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).[13] Spinal cord involvement is rare, and the optic nerves are not involved.[34] Although lesions can be multiple, one lesion is clinically predominant. Initial symptoms and signs usually begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis), as individual lesions expand concentrically or along white matter tracts. Less localized clinical syndromes—such as behavioral changes, dementia, or encephalopathy—result from multiple lesions in the setting of PML and are rarely the presenting clinical phenotype.[35]

The time course of evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral

infarcts begin even more abruptly. Nonetheless, PML is sometimes mistaken for an evolving stroke, which, like PML, is bright on diffusion-weighted magnetic resonance imaging (MRI). Focal brain lesion can mimic strokes; however, the progressive course should make this diagnosis less likely, and PML must be considered. Headache and fever are not characteristic of PML, and when present may indicate presence of another opportunistic infection. Seizures occur in nearly 20% of PML cases and are associated with lesions immediately adjacent to the cortex.[36,37]

Diagnosis

Initial recognition of PML relies on a combination of clinical and neuroimaging findings: steady progression of focal neurological deficits with MRI almost always demonstrating distinct white matter lesions in areas of the brain corresponding to the clinical deficits. The lesions are hyperintense (white) on T2-weighted and fluid-attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences.[2] The T1 findings can be subtle and may help distinguish lesions due to PML from those of other pathologies, including the white matter lesions of HIV encephalitis. A linear, paramagnetic band or rim in the paralesional U-fibers has been described as a common finding in PML and has been proposed to have diagnostic value independent of underlying predisposing disease. Histopathological studies show this band corresponds to iron accumulation within phagocytic cells, although the pathophysiology leading to this remains unclear.[38,39]

Brain imaging with magnetic resonance (MR) or computed tomography is critical to identifying PML and differentiating it from other important treatable diseases that occur in advanced HIV. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident in PML imaging. Although contrast enhancement is present in 10% to 15% of cases, it is usually sparse with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings can occur when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART (see below). Advanced neuroimaging techniques—such as diffusion-weighted imaging (DWI) and MR spectroscopy—may provide additional diagnostic information.[40-42] New PML lesions and the advancing edge of large lesions have a high signal on DWI and a normal-to-low apparent diffusion coefficient, signifying restricted diffusion. These changes relate to regions of active infection and oligodendrocyte swelling. MR spectroscopy can show areas of decreased N-acetylaspartate and increased choline related to axonal loss and cell membrane and myelin breakdown, respectively, with the greatest changes at the center of lesions.[43] Recently, a hyperintense cortical signal seen on MRI scan in non-enhanced T1-weighted cortex images has been associated with seizures complicating inflammatory PML.[37]

In most cases of PML, the combined clinical and radiographic presentations support a presumptive diagnosis. Because the primary treatment method for PML is restoring the patient's immune function, confirming the diagnosis is especially important to ensure ART is initiated rapidly.

JCV DNA is virtually never detected in normal cerebrospinal fluid (CSF) samples. Thus, the usual first step in confirming the diagnosis is to test CSF by polymerase chain reaction (PCR) for the presence of JCV DNA. The assay is positive in approximately 70% to 90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context—namely, subacute onset of focal neurological abnormalities and suggestive imaging findings.[10,44] JCV may be detectable in the CSF of as few as 60% of ART-treated patients.[45] In patients not taking ART, the number of JCV DNA copies can add additional information for prognosis, although the relationship between copy number and prognosis is less clear in patients taking ART.[46,47] CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded. Given that in AIDS patients, multiple opportunistic conditions are sometimes encountered, evaluation of CSF is often indicated to rule out *Cryptococcus*, neurosyphilis,

cytomegalovirus encephalitis, varicella-zoster encephalitis, herpes simplex encephalitis, and tuberculosis. Further, CSF PCR analyses for *Toxoplasma* and consideration of Epstein-Barr virus generally associated with primary CNS lymphoma is often indicated with progressive multifocal brain disease in the setting of AIDS. Because JCV DNA viral load in CSF may be very low even with active PML, highly sensitive PCR performance is desirable. Sensitive assays that detect as few as 50 copies/mL are now available, with some research laboratories exceeding this level of sensitivity; detection of JCV virus in CSF in any amount with the appropriate clinical and imaging findings strongly supports the diagnosis of PML.[48] Analysis of plasma samples for detection of JCV by PCR when positive are relatively specific for PML (~92% in patients with HIV), while the sensitivity is less than 40% in this setting.[49]

In some instances, brain biopsy is required in order to rule out other diagnoses. PML usually can be identified by the characteristic tissue cytopathology—including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages—with identification of JCV or cross-reacting polyoma virus by immunohistochemistry, *in situ* nucleic acid hybridization, or electron microscopy.[13,50,51]

Generally, serologic testing is not useful because of high anti-JCV seroprevalence in the general population. Recently, however, antibody testing has been assessed for stratifying risk of PML with natalizumab treatment.[6] Significant increases in JCV-specific antibody titers[52] and detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing[53] but require further prospective study. The value of anti-JCV antibodies in stimulating Fc receptor-bearing effector cell activity contributing to outcome of PML requires further studies.[54]

Preventing Exposure

Currently, no known way exists to prevent exposure to the virus because most individuals are infected in childhood.

Preventing Disease

In many individuals, JCV infection is likely latent and intermittently productive, although clinically silent, in the kidney or other anatomic sites. Systemic infection may increase in the presence of immunosuppression. It remains a subject of debate whether JCV infection is also latent in the CNS or whether PML results from hematogenous dissemination of infection to the brain resulting in subsequent PML lesion development within months of entry to the CNS.[55,56] Therefore, the only known way to prevent disease is to prevent progression of HIV-related immunosuppression with ART **(AII).**

Treating Disease

Recommendations for Treating and Monitoring PML
Treatment
The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART. • In patients not on ART who are diagnosed with PML, ART should be (re)started immediately (AII). • In patients who are receiving ART but remain viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression (AIII).

• No role for ART intensification in patients with HIV viral suppression (BII). • ART regimens should be selected based on likelihood of achieving virologic suppression and not CPE score (BII). • No effective direct-acting antiviral therapy exists for preventing or treating JCV infections or PML. • The following agents are not recommended for the treatment of PML: cytarabine (AII), cidofovir (AII), interferon-alpha (BIII), interleukin-2 (BIII), topotecan (BIII), pembrolizumab (BIII). • The following agents are not recommended due to limited data: 5HT2a receptor antagonist (e.g., olanzapine, ziprasidone, mirtazapine, cyproheptadine, risperidone) (BIII), mefloquine (BIII). Expert consultation is recommended prior to initiation of these agents. • PML-IRIS may require administration of corticosteroid therapy (BIII). The optimal corticosteroid regimen has not been established but should be tailored to individual patients. ART should NOT be discontinued during PML-IRIS (AIII).
Monitoring
• Timing of follow-up assessments (clinical, lumbar puncture, and MRI) should be guided by clinical progress (BIII). • In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation (BIII). • In patients who clinically worsen before or after this 6- to 8-week period, repeat MRI should be obtained as soon as worsening is recognized (BIII).

Key: ART = antiretroviral therapy; CPE = Central Nervous System (CNS) Penetration Effectiveness; IRIS = immune reconstitution inflammatory syndrome; JCV = JC virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

No specific therapy exists for JCV infection or PML. The main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus.[57] In patients with PML who are not on therapy, ART should be started immediately **(AII).** In this setting, more than half of PML patients with HIV experience a remission in which disease progression stops. Although neurological deficits often persist, some patients experience clinical improvement.[28,29,58-63] In one retrospective study of 118 consecutive patients with PML who received ART, 75 patients (63.6%) survived for a median of 114 weeks (2.2 years) after diagnosis of PML.[63] Neurological function in the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. Another retrospective case series reported that 42% of PML survivors on ART had moderate or severe disability.[64] Peripheral blood CD4 count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm^3 compared with patients who had higher CD4 counts. In other case series, worse prognosis also was associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and presence of lesions in the brain stem.[29,32,59,60,62,63,65] Contrast enhancement on imaging may predict better outcomes, as it is indicative of an immune response to the virus.[31] In multiple sclerosis patients with PML, younger age, more restricted unilobar disease, and lower CSF JCV DNA copy numbers are associated with better outcomes; whether these associations are true for PML in PWH is unknown.[66]

ART should be optimized for HIV virologic suppression in patients with PML who have received ART but remain viremic because of inadequate adherence or ARV resistance **(AIII).** More problematic are patients who develop PML despite successful HIV virologic suppression while

taking ART. A preliminary report of PML with patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher-than-anticipated survival,[67] but it has not yet been followed by structured trial. Therefore, no evidence supports ART intensification for PML **(BII).**

The use of ARV drugs that better penetrate the CNS also has been proposed, with use of the CNS Penetration Effectiveness (CPE) score of drug regimens as a guide. This score is based on the pharmacology of ARV drugs with respect to their chemical characteristics as well as demonstrated entry into the CNS (or, more often, the CSF) and, where available, on their CNS anti-HIV activity.[68] One report found at the beginning of the combination ART era that a high CPE score was associated with longer survival after a PML diagnosis, whereas in the late, more recent ART period, the effect of the CPE score disappeared as more potent ARV regimens led to more effective plasma viral load control.[69] Hence, in the current era, the effectiveness of selecting a treatment regimen with a high CPE score is not established. It seems likely that systemic rather than CNS efficacy is the salient aspect of ART in this setting because ART's most important effect on PML may be restoration of effective anti-JCV immunity that can limit CNS infection.[70,71] ART regimens should be selected based on likelihood of achieving virologic suppression and not CPE score **(BII).**

Several studies have evaluated targeted treatments for PML. However, many anecdotal reports of efficacy have not been confirmed by controlled studies and are therefore not recommended. Based on case reports and demonstration of *in vitro* inhibitory activity against JCV, intravenous (IV) and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither demonstrated clinical benefit.[72] Therefore, treatment with cytarabine is **not recommended (AII).** Similarly, cidofovir initially was reported to have a salutary clinical effect, but several large studies—including retrospective case-control studies, an open-label clinical trial, and a meta-analysis that included patients from five large studies—demonstrated no benefit.[45,61-63,73] Thus, treatment with cidofovir is also **not recommended (AII).**

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as a cellular receptor for JCV in a glial cell culture system,[74,75] drugs that block the 5HT2a receptor, including olanzapine, ziprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,[76] although the rationale for this practice has been questioned.[77] Again, anecdotes about favorable outcomes[1,78-81] have not been substantiated by reports of genuine benefit in larger case series, cohort studies, or formal clinical trials. Thus, at this time, treatment with serotonergic 5HT2a receptor blockers is **not recommended (BIII).**

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,[82] an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some patients, although the outcome likely was little different from the natural course in other patients with AIDS, and the main toxicities were hematologic.[83] At this time, topotecan is **not recommended (BIII).**

A Phase I/II clinical trial of the antimalarial drug mefloquine was initiated based on its demonstrated *in vitro* anti-JCV activity. The trial was later halted by the sponsor because demonstration of efficacy was futile.[84] Mefloquine use for PML treatment is **not recommended (BIII).** Immunomodulatory approaches to the treatment of PML in PWH also have been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival,[85] a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha is **not recommended (BIII).**[86] A single report described failure of interferon-beta treatment of HIV-associated PML[87] and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.[17] Case

reports have described improvement or recovery in PML-related neurological dysfunction in three patients who were not HIV infected and were treated with IL-2: one with Hodgkin lymphoma treated with autologous bone marrow transplantation, one with low-grade lymphoma and allogeneic stem cell transplantation, and one with myelodysplastic syndrome.[88-90] Like the other reports, these too have not been followed up with more substantial trials; therefore, treatment of PML with IL-2 is **not recommended (BIII).** Recent interest in recombinant IL-7 for treatment of PML when CD4 lymphopenia is persistent, sometimes in combination with VP-1 vaccination strategy, are under consideration as an alternative adjuvant immune therapy to improve PML outcomes.[91-95] Checkpoint inhibitor therapy has been considered recently as a means of enhancing the immune response to JCV most commonly in settings outside of HIV where immune reconstitution may be futile. The outcome of reports is conflicting, and further research is required.[96,97] Use of checkpoint inhibitors for PML in the setting of HIV is **not recommended (BIII).**

Adoptive transfer of autologous or allogeneic virus-specific T cells, either against JCV or the closely related BK virus, have been used for the treatment of PML. Across the several small case series published to date, a single patient with HIV-associated PML was treated with benefit.[98-100] Use of disease-specific T cells is actively being explored, but at present cannot be recommended for HIV-associated PML. In summary, immunomodulatory agents are **not recommended (BIII).**

Special Considerations for ART

ART should be (re)started as soon as possible for all patients, ideally before PML develops. For patients with suspected PML, it is especially imperative to start ART quickly **(AII).** For patients already on treatment who have demonstrated plasma HIV viremia and are adherent to therapy, ART should be adjusted, if possible, based on plasma virus susceptibility **(AII).**

Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome)

Treatment response should be monitored with clinical examination and brain MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantification of CSF JCV DNA may prove useful as an index to follow for assessing treatment response. No clear guidelines exist for the timing of follow-up assessments, but it is reasonable to be guided by clinical progress **(BIII).** Often disease progression occurs before stabilization and improvement occurs.[67] In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation to screen for radiographic signs of progression or of immune response and can serve as a further baseline for subsequent scans should the patient begin to deteriorate **(BIII).** In patients who clinically worsen before or after this 6- to 8-week period, repeat neuroimaging should be obtained as soon as worsening is recognized **(BIII).**

PML-Immune Reconstitution Inflammatory Syndrome

PML has been reported to occur within the first weeks to months after initiating ART[2,32,33,101-103] with clinical and radiographic features that differ from classical PML, including lesions with contrast enhancement, edema and mass effect, and a more rapid clinical course.[38,104] As with other presentations of immune reconstitution inflammatory syndrome (IRIS), it is more likely after advanced HIV with low CD4 counts and greater decline in HIV viral load on initiation of ARV. This presentation has been referred to as inflammatory PML or PML-IRIS. Both unmasking of cryptic PML and paradoxical worsening in a patient with an established PML diagnosis have been observed. Histopathology typically demonstrates perivascular mononuclear inflammatory infiltration.[105-108]

Unmasked PML-IRIS is presumed to represent the effects of a restored immune response to JCV infection in the context of ART, with resultant local immune and inflammatory responses.

Because ART-induced immune reconstitution may be associated with both onset and paradoxical worsening of PML, corticosteroids have been used empirically in this setting with reported benefit.[2,102,109] Further study of corticosteroids for treatment of PML-IRIS is needed to confirm efficacy and refine dosage and duration. At present, however, use of corticosteroids to treat of PML-IRIS may be justified in some PML where edema or mass effect causes serious clinical deterioration **(BIII).** The decision to use steroids can be difficult because it is the immune response to JCV that controls the infection and treatments that blunt that response could be deleterious. Nevertheless, the inflammatory response against PML can, at times, be more damaging than the virus itself, and corticosteroids appear to have a role in treatment of these patients.

The dosage and duration of corticosteroids for PML-IRIS have not been established. In the absence of comparative data, adjuvant corticosteroid therapy should be tailored to individual patients. One approach, modeled on treatment of multiple sclerosis flairs, is to begin with a 3- to 5-day course of IV methylprednisolone dosed at 1 g per day, followed by an oral prednisone taper, dosed according to clinical response. A taper may begin with a dose of 60 mg per day in a single dose, tapered over 1 to 6 weeks. Clinical status should be monitored carefully during this taper in an attempt to minimize systemic and immune effects while avoiding IRIS recrudescence. Contrast-enhanced MRI at 2 to 6 weeks may be helpful in documenting resolution of inflammation and edema and to obtain a new baseline, recognizing that the MRI appearance may worsen despite clinical improvement and that clinical status is likely the best indicator of treatment efficacy. Importantly, ART should be continued **(AIII).**

Several case reports suggest that maraviroc might be beneficial for PML-IRIS,[110] presumably related to the immunomodulatory rather than ARV properties of the CCR5 inhibitor. However, no comparative studies in HIV-associated PML have confirmed benefit of including of maraviroc in HIV therapy in this setting.[110,111] A retrospective cohort study of 27 patients with PML in whom maraviroc was used failed to show utility in preventing PML-IRIS.[112] Maraviroc is not recommended as a component of treatment of PML **(BIII).**

Managing Treatment Failure

PML remission can take several weeks, and no strict criteria exist to define treatment failure. However, a working definition of treatment failure may be continued clinical worsening after 3 months of ART initiation. Changes in plasma HIV RNA levels and blood CD4 count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for the use of ART (see Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines). When PML continues to worsen despite fully suppressive ART, one of the unproven therapies described above could be considered after consultation with an expert **(CIII),** although the possibility of toxicity must be balanced against the unproven benefits of these treatments. The search for other potentially treatable comorbid conditions, like hepatitis C virus and associated cirrhosis, also should be considered in this setting.[113]

Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence unless ART is interrupted.[61,114] The main preventive measure, based on its role in reversing the disease, is treatment with an effective ART regimen that suppresses viremia and maintains CD4 counts **(AII).**

Special Considerations During Pregnancy

During pregnancy, the diagnostic evaluation of PML should be the same as in any other person with HIV. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen.

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