Progressive Multifocal Leukoencephalopathy in HIV Infected and Non-HIV Subjects: Evolving Concepts and Disease Patterns

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Progressive multifocal leukoencephalopathy (PML) is a rare, serious, and usually fatal demyelinating disease caused by human polyomavirus (JCV). The incidence of this opportunistic infection has risen dramatically during the AIDS epidemic.

In the West over 50% of healthy adolescents and adults have serological evidence of primary polyoma viral infection, probably acquired by oral or respiratory route. From India similar serological data is not available. JCV persists as a latent and asymptomatic infection in B lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state with CD4 count < 100 lymphocytes, kidney and possibly central nervous system (CNS). Immunosuppressive state. JCV reactivates the latent infection causing viremia and CNS disease, although 11% had CD4 + cell counts > 200 cells/mm³ in one series. Clifford and colleagues reported a wide range plasma HIV viral load values in patients with PML, with a mean of 3362 copies/mL. However, one third of patients had undetectable viral load.

In immunosuppressed patients, JCV becomes activated, resulting in viremia and dissemination to the CNS, either in cell-free or cell-associated form. Within the CNS, JCV productively infects oligodendrocytes, leading to demyelination and clinical disease. The lesion is preferentially localized to gray-white junction of the cerebral hemisphere and manifests as characteristic demyelinating lesion, called scalloping. Isolated lesions of the cerebellar hemispheres and/or brain stems have also been observed. JCV can also infect immune progenitor cells, which supports the hypothesis that JCV acts by a "Trojan horse" mechanism in transiting from the periphery to the brain. The receptor for JCV includes the serotonergic 5-hydroxytryptamine receptor 2A, which is found on astrocytes, glial cells, B cells, and kidney epithelial cells. However, binding itself does not appear to be a critical step in establishing productive infection. The ability of JCV to infect CNS glial cells is contingent upon rearrangement of the viral transcription control region and upon intracellular DNA binding proteins that direct gene expression from the rearranged TCR.

Significant genetic diversity of JCV has been identified in various geographic regions around the world, with variable permissiveness infecting, the glial elements. HIV-I virus infecting the population of India and sub-Saharan Africa belongs to the subtype c elade C, while in USA, Europe, Australia, and Japan it is HIV-I elade B. These two subtypes differ on their genetic constitution of the HIV virus and trans activating property on co-existing JCV. This may explain the low prevalence of PML in India and Sub Saharan Africa.

Patients with PML present with insidious disturbances in motor function, vision, or mental status that progress. The most frequent visual deficits are homonymous hemianopia or quadrantanopia due to lesions in the optic radiations or occipital cortex. Optic nerve involvement is not seen, and spinal cord involvement is extremely rare. Seizures are a manifestation of gray matter or cortical dysfunction, and their occurrences is not expected in the setting of a leukoencephalopathy, but new-onset seizures have been reported in patients with PML. In the pre-HIV era, seizures in PML were unusual, but in more recent series, seizures have been initial manifestation of PML in 18% patients. Simple partial seizures, complex partial seizures as well as partial onset with secondary generalisation have been documented in PML cases. Because 80% of the patients who develop PML have HIV infection or other severe illnesses, polypharmacy is common in this population. Pharmacologic interactions should be taken into account when choosing AEDs. Levetiracetam is excreted unchanged in the urine, has few interactions with other drugs, and is effective for different types of seizures.

For confirmation of diagnosis of PML brain biopsy specimens are obtained. The characteristic histological features are foci of demyelination rimmed by inclusion bearing oligodendrocytes and bizarre astrocytes of variable morphology. Immunohistochemistry and electron microscopy establishes the diagnosis when anti-JCV specific antibody labeled the inclusions and the viral antigen are noted in astrocytes. In absence of brain biopsy specimens, serological diagnosis against the JC virus is necessary for laboratory confirmation.

The presence of antibodies to JC virus does not alone support a diagnosis of PML, because 80% of the human population is seropositive. Renal JC virus DNA carries the archetype regulatory region, whereas the CNS JC virus DNA of PML patients contain various regulatory regions, so called PML-type regulatory regions. PCR analysis to identify...
JC virus DNA with PML-type regulatory region sequences in CSF has been reported to be useful for diagnosing PML with high sensitivity and specificity (82% and 100%, respectively). PML-type regulatory regions are generated from the archetype by deletions and/or duplications in infected individuals after the primary infection, and they differ from patient to patient. 

A recent study has shown that JC virus DNA levels in cerebrospinal fluid of patients with HIV associated progressive multifocal leukoencephalopathy has prognostic significance. High JCV DNA levels in CSF samples obtained early in the course of PML were shown to be a predictive marker of poor survival in patients with PML and were associated with low CD4+ cell counts only in HIV infected patients who were not treated with highly active antiretroviral therapy (HAART). However, a reduction or suppression of the JCV DNA burden in the CSF of patients receiving HAART was associated with stabilization of PML, irrespective of plasma HIV RNA levels and CD4+ cell count responses to treatment. 

The sensitivity and specificity of PCR detected JCV in the CSF have not been prospectively determined in non-HIV cases of PML. 

In this issue of the Journal Raina et al. describe a case of a 45 years old male patient whom they have diagnosed to have PML based on the suggestive clinical features and brain imaging findings. JC virus PCR studies in CSF was not done in this patient. Hence according to recommended consensus terminology, this case can be classified as a case of “possible” PML in HIV infected person. Very few proven cases of PML in HIV infected cases are reported form India. The PML cases are referred as 

a) Histology-confirmed with evidence of JCV infection in brain.

b) Laboratory-confirmed with detection of JCV-DNA in CSF.

c) Possible with in the presence of typical clinical and radiological picture but no demonstration of JCV infection.

Amongst the several neuroimaging modalities available to visualize structural and functional abnormalities of brain, MRI has greater sensitivity than other imaging modalities. In the appropriate clinical context, brain MRI will support the diagnosis of PML.

The lesions are usually multifocal, bilateral, asymmetric involving the periventricular and subcortical white matter with a scalloped lateral margins more often in the parieto-occipital lobes, hyperintense on the T2 FLAIR. The basal ganglia and deep grey nuclei can be involved. Posterior fossa involvement is seen in up to 1/3rd cases. There is typically no enhancement but faint peripheral or diffuse enhancement with mass effect may be seen especially in the early stage. Spinal cord involvement and optic nerve affection is rare. Diffusion weighted MR images shows areas of restricted diffusion associated with rapid progression of PML. Enhancing lesions in HIV-positive patients with PML receiving HAART are correlated with a better prognosis. However patient on HAART may show initial worsening followed by stabilization and regression. Spread of the disease to the corpus callosum, increasing atrophy, increasing confluent and extent of white matter lesions, increasing hypo intensity of the lesion on T1W images on the follow-up scans are poor prognostic indicator or failure of response to therapy. Stabilization or decrease in size of the lesions associated with clinical improvement and loss of JC virus detected on CSF PCR may indicate response to therapy. Improvement on MRI can lag by 2-6 months. Resolution of diffusion abnormality is observed in PML survivor. Mass effect is significantly associated with shorter survival.

Biochemical changes within living brain tissue can be examined by Magnetic Resonance Spectroscopy (MRS). This produces very different results from other MR techniques in that it provides information about the neurochemical composition of the tissue within a designated region of interest. Spectroscopy is most often added to an MRI scan as an extra series and adds approximately seven minutes or more to the duration of the scan, depending on the number of regions of interest that are examined. It is generally sensitive to the presence of neurochemicals with fairly high concentrations. MRS results are displayed in form of spectra with peaks representing concentrations of various brain metabolites. 

MRS is nonspecific for PML with generalized decrease in NAA and creatine with increased levels of choline and myoinositol in the early phase. Lactate may be present. In the late phase all the metabolites are reduced. The changes of these chemical markers correlated with the clinical course. 

In the era before acquired immunodeficiency syndrome, PML was most commonly associated with chronic lymphocytic leukemia, Hodgkin’s lymphoma, organ transplants, and sarcoidosis. Recently, PML has been reported in patients with Crohn’s disease and multiple sclerosis with the use of natalizumab, a humanized monoclonal antibody against integrins (adhesion molecules). Natalizumab appears to distinctively predispose recipients to PML relative to other infectious complications.

On December 18, 2006 the US Food and Drug Administration (FDA) in conjunction with Genentech and Biogen Idec, the makers of rituximab, a recently approved biologic agent for the treatment of RA, issued a warning to health care providers, informing them that 2 patients receiving rituximab for the treatment of SLE had developed PML. Rituximab is a monoclonal antibody to the B cell lineage antigen CD20 that has been approved for the treatment of non-Hodgkin’s lymphoma and more recently, for RA in which treatment with one or more tumor necrosis factor antagonists has failed. PML has been reported in rituximab-treated oncology patients on 23 occasions, with the majority having received rituximab in combination with multiagent chemotherapy or stem cell transplantation.

Recent reports have highlighted that PML can occur in patients with rheumatic diseases, particularly in the current era of biologic therapy for autoimmune disorders. Thirty five cases of PML in patients with rheumatic diseases have
been published so far, 22 of these were in SLE patients. The remaining 13 patients had rheumatoid arthritis (RA) polymyositis/dermatomyositis. Wegener’s granulomatosis and systemic sclerosis.10

Differentiating PML from the new onset or exacerbation of CNS complications in various rheumatic diseases can be problematic. Clinical history and physical examination remain the most important discriminators between PML and neuropsychiatric SLE or CNS vasculitis. Optic nerve or spinal cord involvement is extremely rare in PML and is strong evidence against this diagnosis. Diagnostic difficulties are particularly salient for acute neuropsychiatric SLE and CNS vasculitis. The importance of differentiating PML from these conditions is underscored by the fact that initiating or escalating immunosuppressive therapy, which is beneficial in immune-mediated CNS disease, is the diametrically opposite treatment strategy for PML, which is aimed at restoring host defenses whenever possible.10

HAART has improved the clinical outcome in PML in HIV infected patients with long periods of remission. It acts indirectly by its antiretroviral action, increase CD4+ counts and thereby immunological function. Conversely patients already on HAART who develop PML within the immune reconstitution period fare poorly. Several factors have been proposed as prognostic markers for the course of PML, including CD4+ cell count, radiologic appearance of the lesions (i.e. degree of contrast enhancement), degree of inflammation on histologic specimens, and level of JC virus DNA in CSF. Clifford and colleagues24 have reported that suppressed plasma HIV viral load is the strongest indicator of an improved disease course. While the mean survival of patient with PML was approximately 3-4 months in the pre HAART era, it is not uncommon for patients whose plasma HIV viral load has been suppressed by HAART to survive for years with stable neurologic status.24,25

Several rheumatic disease patients with PML have survived after withdrawal of immunosuppressive therapy and initiation of cidofovir, interferon, or cytarabine treatment, but in no case was there a clear therapeutic associated with significant sequelae.23 Clearance of JCV from the CSF and/or development of enhancement around existing white matter lesions on neuroimaging may be indicators of recovery.

References