

Progressive multifocal leukoencephalopathy: JC virus induced demyelination in the immune compromised host

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Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the central nervous system that predominantly affects immunocompromised individuals. The etiologic agent, JCV, is a widespread polyomavirus with a very specific target, the myelin-producing oligodendrocytes of the brain. During periods of immune suppression, the virus can be reactivated from lymphoid tissues and kidney, causing targeted myelin destruction and corresponding neurological deficits. The incidence of PML has increased in recent years, due in large part to the advent of AIDS and the growing number of immunodeficient individuals. Furthermore, previous serological studies have shown that greater than 80% of the human population has antibodies to JCV in circulation. When combined, these statistics highlight an increasing need to establish effective treatment regimens for infected individuals as well as strategies to identify those at risk for developing PML. *Journal of NeuroVirology* (2000) 6, S98–S100.

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Opportunistic infections associated with immunosuppressive disorders have become a great concern for physicians and researchers alike. The AIDS pandemic has resulted in a rapid increase in the number of immune deficient individuals with a corresponding increase in the incidence of complicating illnesses. Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection caused by demyelination in the white matter in the brain. Once considered rare, PML is now frequently being observed in association with HIV infection. It is estimated that 85% of reported PML cases have AIDS as the underlying immune deficit (Berger and Concha, 1995), and that 6% of all AIDS patients will eventually develop the disease (Major and Curfman, 1997). The etiologic agent, JCV, is an ubiquitous human papovavirus that specifically targets the myelin producing oligodendrocytes. Approximately 80% of the human population

worldwide has antibodies to JCV circulating in the peripheral blood (Padgett and Walker, 1973). It is postulated that after initial infection early in life, the virus remains latent and is only reactivated during periods of immune compromise. The ensuing lytic infection causes areas of demyelination in the brain which manifests as neurological deficits consistent with such white matter destruction.

The pathology of PML is caused by the cytolytic destruction of oligodendrocytes, resulting in lesions that appear initially in a sparse, asymmetric distribution. With disease progression, the foci of demyelination or plaques can enlarge to a few centimeters across and coalesce, making them visible in the brain upon gross anatomical examination. The periphery of the lesions contains astrocytes and oligodendrocytes that may be infected with JCV, but have not yet undergone lysis. The morphology of these cells is characteristic of this disease with nuclei 2–3-fold larger than normal, and often containing inclusion bodies. Electron microscopy of the intranuclear inclusions reveals a dense array of JCV virion particles, arranged in a crystalline lattice. Other pathologic features of this disease include bizarre, enlarged astrocytes and

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mononuclear cell infiltration. Macrophages swollen with lipids can often be found in the lesioned areas, evidence of myelin degradation. However, recruitment of other cells involved in inflammation is rarely observed.

Neuroimaging studies have been useful in determining the location and extent of the demyelinated plaques. Computerized tomography (CT) and magnetic resonance imaging (MRI) are the most frequently used methods of visualization. The lesions are typically non-contrast enhancing and periventricular in nature, most often located at the gray-white matter junction. Although the lesions can occur anywhere in the subcortical white matter, they appear most frequently in the parietooccipital or frontal lobes. In comparison with CT scans, MRI is the more sensitive; often revealing PML pathology where CT scans appeared normal. The extent of lesioning is also demonstrated more clearly by MRI because it is capable of detecting lesions located in the cerebellum, which is of particular interest since there has been a recent rise in reports of PML lesions located in the posterior fossa (Takahasi *et al*, 1992; Sweeney *et al*, 1994).

Neurological manifestations of JCV induced tissue damage include visual, motor, and cognitive impairments, the classic triad of presenting symptoms for PML. Hemianopsia, or the loss of vision in one half of the visual field, is the most common, accounting for 40% of all initial presentations (Berger and Major, 1999). Cortical blindness may also be present in a small percentage of patients at the time of initial diagnosis. Severe muscle weakness progressing into hemiparesis or hemiplegia is also reported in greater than 50% of cases. This lack of voluntary muscle coordination often manifests itself in the form of gait disturbances or loss of balance. In addition, altered mentation eventually affects most patients diagnosed with PML (Major *et al*, 1992). Deterioration of cognitive functions may be rapid, leading to confusion, extreme emotional lability, and ultimately, dementia.

JCV genome and viral proteins can be detected in tissue sections by *in situ* hybridization and immunohistochemistry, respectively. Hybridization of a specific biotinylated JCV DNA probe to complementary strands in the tissue is followed by colorimetric detection of the probe by streptavidin-horseradish peroxidase conjugate (Houff *et al*, 1989). Using this technique, JCV DNA has been visualized in both the enlarged and normally sized nuclei of infected oligodendrocytes, astrocytes, and B lymphocytes (Jensen and Major, 1999). Because viral genomes must be present in relatively high copy numbers to generate a positive signal, *in situ* hybridization identifies cells that are not only infected, but are also undergoing active viral DNA replication. JCV proteins have been identified in cells using antibodies against the viral, non-structural T protein and capsid antigens (V pro-

teins). The presence of the capsid antigen determines productive infection, demonstrating full genomic transcriptional and translational activity in infected cells. Immunocytochemical staining has revealed viral proteins in oligodendrocytes as well as in astrocytes, tonsillar stromal cells, and B lymphocytes (Jensen and Major, 1999). Initial studies were hindered by the lack of an antibody specific to JCV. However, there are now monoclonal antibodies available that show no cross-reactivity with BKV or SV40, both of which share significant nucleotide and amino acid homology with JCV.

Polymerase chain reaction (PCR) has gained great interest recently because of its routine but highly sensitive detection of low copy numbers of JCV. PCR amplification of DNA extracted from peripheral blood and CSF has yielded interesting results. On average, 50% of HIV seropositive patients have detectable levels of JCV in their peripheral blood showing a range from 20 to 89%. Surprisingly a high number of healthy individuals have JCV DNA in their peripheral blood supporting the theory that the majority of the population is latently infected (Tornatore *et al*, 1992). The possible diagnostic value of PCR is supported by results showing that JCV genome was present in the CSF of more than 80% of AIDS patients with PML, as opposed to negative results in the CSF of control groups (Weber and Major, 1994). Detection of JCV DNA in the CSF of healthy individuals is rare, and may be considered false positive results. Despite the sensitivity and specificity of the assay, however, a definitive diagnosis of PML benefits from the demonstration of JCV DNA in brain biopsy sections, which can then be supported by PCR results.

The ubiquitous nature of JCV and its high concurrence with HIV-1 infection has increased efforts in finding effective treatment and prevention strategies against PML. Because the majority of reported cases occur in AIDS patients, it was postulated that treating the underlying immune deficit would alleviate symptoms of PML as well. To this effect, there have been case reports describing resolution of clinical symptoms as a result of antiretroviral drugs, alone and in a combination otherwise known as Highly Active Retroviral Therapy, or HAART. Observational studies have shown that in patients with HIV associated PML, HAART therapy significantly extended their survival times after initial diagnosis, as compared to a group of historical controls (Albrecht *et al*, 1998; Clifford *et al*, 1999). Administration of nucleoside analogs has also been reported to stabilize disease progression. Specifically, reports of clinical remission following cytarabine therapy prompted a multicenter trial investigating the efficacy of Ara-C in patients with PML (Hall *et al*, 1998). The results showed that administration of Ara-C did not significantly improve the prognosis of individuals receiving the

therapy. However, further investigations of Ara-C with alternative delivery methods are currently being pursued. Other potential therapies for PML include cidofovir, a non-cyclic nucleoside analog. Similar to Ara-C, antiviral activity is conferred by inhibition of chain elongation during DNA repli-

cation. Initial case reports have been encouraging, demonstrating clinical as well as neuroradiologic and virologic remission (Blick *et al*, 1998; De Luca *et al*, 1999). A clinical trial is currently underway to further investigate the efficacy of cidofovir against PML.

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