Progressive Multifocal Leukoencephalopathy (PML)

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Introduction:
Progressive multifocal leukoencephalopathy (PML) occurs when change in an individual’s immune status triggers reactivation of a latent viral infection. Reactivation of the virus leads to destruction of oligodendrocytes and astrocytes resulting in white matter lesions and cognitive decline.² ¹⁰

Etiologic Agent:
The JC virus (JCV) causes PML. PML occurs as an opportunistic infection in individuals with AIDS or cancer. Treatment with immunotherapy or immunosuppressive drugs, such as in multiple sclerosis, Crohn’s disease, and organ transplants can also lead to PML.⁵ ¹⁰

Reservoirs:
JCV exclusively infects humans. The virus is ubiquitous; an estimated 40-90% of all healthy individuals carry antibodies to the virus in their blood.² Initial infection is thought to occur in childhood and is generally asymptomatic.¹⁰

Disease Transmission:
JCV infection likely occurs through airborne transmission. A potential host inhales the virus which attaches to tonsil cells. B lymphocytes within the tonsils are thought to carry the virus through the body where it settles in the kidneys and bone marrow and remains latent. The virus can be shed in the urine and become aerosolized.² ¹⁰

Due to increased permeability of the blood brain barrier caused by disease process or immunotherapy, the virus may cross the blood brain barrier via lymphocytes. Here, the virus enters a lytic phase and destroys myelin producing oligodendrocytes, and astrocytes.⁵

Characteristics/Taxonomy of JCV:
JCV is a non-enveloped, icosahedral, double-stranded DNA virus.⁴ JCV belongs to the Polyomaviridae family and Betapolyomavirus genus.⁶

JCV’s genome contains two coding regions. The early transcription region codes for the large (T-Ag) and small tumor (t-Ag) antigen proteins. The late transcription region codes for JCV’s three capsid proteins (VP1, VP2, and VP3), accessory protein agnoprotein, and various regulatory proteins.⁴ ⁸ ¹³
Historical Information:
JCV was first isolated in the 1970’s from the brain of a Hodgkin Lymphoma patient who died of PML. The patient’s initials give the virus its name.\(^4\)

PML was historically associated with lymphoproliferative disorders.\(^5\) However, an increase in the number of PML cases corresponded with the AIDS pandemic of the 1980’s and increased use of medications that suppress or modulate the immune system.\(^4,^5\) Of total PML cases it is estimated that “80% of PML patients have AIDS, 13% have hematological malignancies, 5% are transplant recipients, and 2% have chronic inflammatory disease.”\(^9\)

Signs and Symptoms:
Initial symptoms of PML may mimic a stroke or progression of multiple sclerosis.\(^5\) PML commonly presents with changes in vision, emotional disturbances, memory problems, and motor weakness that progressively become worse.\(^5,^10\) PML patients may also experience aphasia and seizures.\(^5\)

Virulence Factors:
VP-1, a capsid protein, binds specifically to sialic acid containing structures on the surface of host target cells and initiates endocytosis.\(^5\)

Agnoprotein is thought to modify the plasma membrane permeability of virally infected cells. The increased permeability allows for an influx of Ca+ ions that further disrupts the plasma membrane and assists mature virus particles in exiting the cell.\(^11\)

JCV directs infected cells to produce T antigen proteins. These proteins are thought to initiate S phase in the infected cell leading to efficient replication of the virus.\(^5,^7,^10\)

Tests for Identification:
PML diagnosis is based on presence of pathological changes to brain tissue and the presence of JCV in the cerebral spinal fluid or brain tissue.\(^1,^5\)

A triad of cytopathic effects associated with PML can be seen using light microscopy: enlargement of the nucleus in infected oligodendrocytes, enlarged astrocytes, and multifocal lesions. CT and MRI imaging reveal multifocal, often scalloped white matter lesions.\(^1\)
PCR based assays can detect the presence of JCV’s T-Ag protein in cerebrospinal fluid or brain biopsy samples. Contamination of cerebrospinal fluid with blood can lead to false positive reactions, as viremia can occur with JCV.\(^1\)

Flow cytometry can detect immunolabeled T-Ag.\(^7\) Additionally, monoclonal antibodies directed against JCV’s T-Ag protein and labeled with a stain can be used to detect JCV in brain biopsy samples.\(^8\)

**Control/Treatment:**
PML has a 3 month mortality rate of up to 50%; prompt diagnosis is essential. Treatment involves restoring the function of the immune system-- either by discontinuing immunomodulating drugs or, in the case of HIV/AIDS, treatment with antiretroviral medication. Plasma exchange transfusion may help clear immunomodulating drugs from the body.\(^2\)

Restoration of the immune system can clear virus infected cells from the brain and halt the progression of PML. However, withdrawal of immunomodulating therapies is not without risk. Immune Reconstitution Inflammatory Syndrome (IRIS) can occur when the immune system resumes normal function leading to an influx of white blood cells into the brain. IRIS causes a temporary worsening of PML symptoms.\(^2, 3\)

**Clinical Trials:**
The National Institute of Neurological Disorders and Stroke is preparing a clinical trial for a PML immunotherapy. Researchers intend to treat PML patients with polyoma virus-specific T cells harvested from a relative.\(^12\)

**Local Outbreaks:**
The incidence of PML in patients treated with various immunotherapy drugs has been tracked by the United States Food and Drug Administration’s Adverse Events Reporting System (FAERS). In 2017, there were 48 cases of PML associated with Natalizumab and 52 cases associated with Rituximab.\(^14\)

**Global Outbreaks:**
Since 1998, there have been 61 cases of Natalizumab-associated PML and 57 cases of Rituximab-associated PML in the United Kingdom.\(^15, 16\) As of 2013, there have been 108 cases of suspected PML in Sweden. Of the Swedish PML patients, 24% received treatment with either Natalizumab or Rituximab.\(^17\)

Natalizumab’s global PML incidence is estimated at 3.85 cases per 1,000 patients who have received 25 or more doses.\(^5\)
Works Cited:


