

# Progressive Multifocal Leukoencephalopathy in an HIV-Negative Patient following Treatment with Rituximab

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**P**rogressive multifocal leukoencephalopathy is a rare and lethal demyelinating disease of the central nervous system. It is associated with reactivation of the JC virus in immunocompromised patients. PML may affect HIV/AIDS patients but can also result from the use of potent immunosuppressive regimens and novel biological therapies. This observation raises concerns about the safety profile of these agents.

Rituximab is a chimeric anti-CD20 monoclonal antibody commonly used in the treatment of lymphoproliferative malignancies. The development of PML following rituximab treatment has been reported rarely. We report here a case of PML in an HIV-negative patient with diffuse large B cell lymphoma following treatment with rituximab. Diagnosis was based on clinical findings as well as imaging and direct demonstration of the JC virus in the cerebrospinal fluid.

## PATIENT DESCRIPTION

A 66 year old man presented to the hospital with progressive confusion, agitation and functional deterioration. His past

medical history included chronic renal failure, ischemic heart disease, bipolar disorder, and a 1 year history of stage IV diffuse large B cell lymphoma. He had received five cycles of chemotherapy with the R-CHOP protocol (rituximab, cyclophosphamide, adriamycin, oncovin, prednisone) 7 months prior to his current admission with a good clinical and radiological response. A sixth cycle of chemotherapy was withheld due to persistent and prolonged neutropenia.

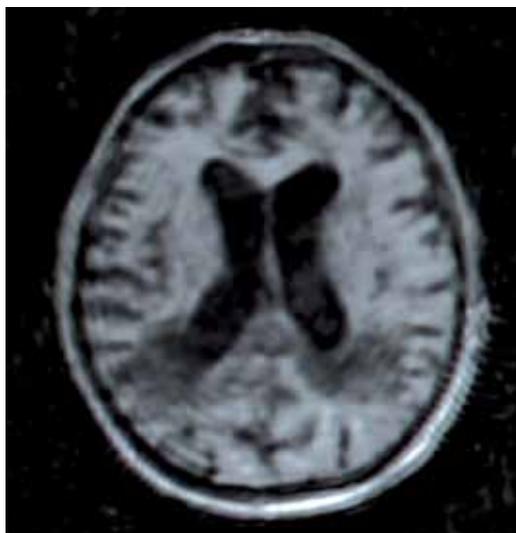
His physical examination was remarkable for confusion without focal neurological deficits. Laboratory examination revealed pancytopenia (white blood cells 0.92 K/ $\mu$ l, hemoglobin 8.9 g/dl, platelets 102 K/ $\mu$ l) and mild renal failure (creatinine 1.4 mg/dl, urea 52 mg/dl). Blood electrolytes, thyroid-stimulating hormone and B12 levels were within normal limits. An HIV test was negative and a computed

tomography scan of the brain was normal. CSF analysis was normal and showed no cells. Bone marrow biopsy revealed mild hypocellularity. A PET scan (positron emission tomography) showed no signs of active hematological disease. Three weeks later further deterioration was noted in the patient’s mental status and he became non-responsive. Polymerase chain reaction for JC virus from the CSF returned positive. Magnetic resonance imaging of the brain showed white matter abnormalities consistent with progressive multifocal leukoencephalopathy [Figure]. The patient died a few days later.

## COMMENT

PML is a white matter disease caused by reactivation of the JC virus. The JC virus

CSF = cerebrospinal fluid



MRI showing changes consistent with PML. Diffuse bilateral hemispheric changes in white matter are prominent on DW1 without enhancement or mass effect

PML = progressive multifocal leukoencephalopathy  
HIV = human immunodeficiency virus

is a double-stranded DNA virus named for John Cunningham, the individual from whom the virus was first isolated. Between 66% and 92% of the adult population is seropositive for the JC virus. The primary infection is thought to occur in childhood through the respiratory and gastrointestinal tracts. After the primary asymptomatic infection, the virus remains latent in different sites including the kidney, bone marrow and B lymphocytes. Despite its presence in multiple sites, only severe immunosuppression can enable the virus to translocate into the brain, infecting oligodendrocytes and causing PML.

The history of PML has been characterized by three distinct landmarks. In the past, PML was a disease of patients with hematological malignancies treated with chemotherapy. Then, in the 1980s, it emerged predominantly as a complication in AIDS patients, prior to the era of the highly active antiretroviral therapy. In recent years, however, the observation of PML after using biological therapies has been of special concern.

Rituximab is a chimeric anti-CD20 monoclonal antibody widely used in the treatment of lymphoproliferative malignancies. The development of PML following treatment with rituximab is exceedingly rare. It has been hypothesized that rituximab facilitates the development of PML through the depletion of mature B cells. Consequently, the decrease in mature B cells induces expansion of pre-B cells infected with latent JC virus. These lymphocytes carry the virus to the central nervous system where it infects and destroys oligodendrocytes [1].

The diagnosis of PML is based on clinical neurological findings, positive PCR for the JC virus from CSF, characteristic findings on MRI, and brain biopsy. The latter, however, is seldom required for the diagnosis. Neurological signs and symptoms may be either focal or diffuse. The PCR for

JC virus should be obtained from cerebrospinal fluid. Fong et al. [2] showed that the sensitivity and specificity for JC virus DNA by PCR were 74% and 96%, respectively. MRI of the brain has a strong negative predictive value. Typical radiographic characteristics of PML on MRI include subcortical white matter hyperintense areas on T2-weighted images. On T1-weighted images hypointense lesions can be seen that usually do not enhance [3].

The management of PML depends on the clinical setting. In HIV patients not treated with an antiviral agent, initiation of HAART is essential. In patients receiving immunosuppressive medications, immune reconstitution should be accelerated primarily by withdrawal of immunosuppressive therapy. Nevertheless, PML remains an incurable disease. Different treatments have been tried over the years with no significant success [3].

Carson et al. [4] reviewed 57 cases reported during the years 1997–2008. They analyzed PML case descriptions among patients treated with rituximab. The clinical data were provided by the Food and Drug Administration, the manufacturer, physicians and a literature review. They reported a 5.5 months median time from the last rituximab dose to diagnosis of PML and a 2 months median time from PML diagnosis to death [4]. In the patient described here, the diagnosis of PML was made 8 months after completion of rituximab treatment and his death occurred soon afterwards.

This communication highlights the awareness required for a possible diagnosis of PML in individuals receiving rituximab. The relevant differential diagnosis for the behavioral changes in this case also included central nervous system lymphoma and a non-organic etiology (given his psychiatric background). However, detection of JC virus in the CSF in the relevant clinical setting was diagnostic

for PML and magnetic resonance imaging confirmed the diagnosis.

Although PML in this patient could be hypothetically related to other chemotherapeutic agents or lymphoma, we believe that rituximab remains a more likely cause. First, the presentation of PML occurred 8 months after the last treatment, which is compatible with the previously reported time for this complication. Second, the patient attained complete remission and was disease-free at the time of PML diagnosis.

In this era of widespread use of biological agents it is prudent to keep the diagnosis of PML in mind and to actively seek JC virus in the appropriate clinical setting. Recently, a study on risk factors for PML after treatment with natalizumab, a monoclonal antibody against alpha-4 integrin, was published in the *New England Journal of Medicine* [5], and it is anticipated that the number of reports will continue to grow with the accumulation of additional data on these drugs.

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#### References

1. Bellizzi A, Nardis C, Anzivino E, et al. Human polyomavirus JC reactivation and pathogenetic mechanisms of progressive multifocal leukoencephalopathy and cancer in the era of monoclonal antibody therapies. *J Neurovirology* 2012; 18: 1-11.
2. Fong IW, Britton CB, Luinstra KE, Toma E, Mahony JB. Diagnostic value of detecting JC virus DNA in cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. *J Clin Microbiol* 1995; 33: 484-586.
3. Calabrese L. A rational approach to PML for clinicians. *Cleve Clin J Med* 2011; 78: S38-41.
4. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from research on adverse drug events and report project. *Blood* 2009; 113: 4834-40.
5. Bloomgren G, Richman S, Hoterman C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012; 366: 1870-80.

PCR = polymerase chain reaction

HAART = highly active antiretroviral therapy

**“Common sense is the fountainhead of Justice”**

Ronald W. Stone, American judge