Progressive Multifocal Leukoencephalopathy Following Treatment with Rituximab in an HIV-Negative Patient with Non-Hodgkin Lymphoma

A Case Report and Literature Review

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Key words: progressive multifocal leukoencephalopathy, JC virus, follicular non-Hodgkin lymphoma, rituximab

SUMMARY – *Progressive multifocal leukoencephalopathy (PML) is a rare rapidly progressive demyelinating disease of the central nervous system caused by reactivation of latent John Cunningham (JC) polyomavirus (JCV) infection. We describe an unusual case of PML in a 54-year-old patient with follicular non-Hodgkin lymphoma who received rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovicin and prednisolone (R-CHOP) therapy. She started to notice gradual progressive neurological symptoms about two months after completion of rituximab treatment and was therefore admitted to hospital. On admission, brain CT and MRI showed widespread lesions consistent with a demyelinating process involving the subcortical and deep white matter of the cerebral and cerebellar hemispheres. CT and MRI findings were suggestive of PML, and JC virus DNA was detected by polymerase chain reaction assay of the cerebrospinal fluid and serum. The patient was treated supportively but reported a progressive worsening of the clinical and radiological findings. Our report emphasizes the role of CT and MRI findings in the diagnosis of PML and suggests that PML should be considered in patients with progressive neurological disorders involving the entire nervous system and mainly the white matter, especially in the presence of previous immunomodulatory treatment or immunosuppression.*

Introduction

Progressive multifocal leukoencephalopathy (PML), a rare demyelinating disorder of the central nervous system (CNS), is associated with high rates of morbidity and mortality¹. PML is an opportunistic infection resulting from reactivation of latent John Cunningham (JC) polyoma virus (JCV)². JCV is a ubiquitous polyomavirus infecting 50% or more of the adult population throughout the world, but PML remains an extraordinarily rare complication of this infection in otherwise normal persons and

almost always occurs in the setting of predisposing immunosuppressive conditions³.

From 1958 to the 1980s, PML was observed mostly in patients being treated with corticosteroids, other immunosuppressive drugs and chemotherapy⁴. Then, in the 1980s it emerged predominantly as a complication in AIDS patients⁴. Recently, the use of new immunomodulatory and immunosuppressive drugs may increase the risk for the development of disorders arising in the setting of immunosuppressive conditions⁵. Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody commonly used

Figure 1 Initial MRI images obtained some days after the onset of neurological symptoms (January 2014). Axial FLAIR did not show any significant alterations.

Figure 2 CT obtained on admission (February 2014) showed multiple hypodense lesions in the white matter of the cerebral and cerebellar hemispheres.

in the treatment of haematologic malignancies and non-malignant autoimmune disorders⁶.

The approach to diagnosis of PML has evolved considerably since its initial description in 1958 when the diagnosis of PML was predicated on brain histopathology³. Now, the presence of classic radiographic findings and clinical features consistent with the diagnosis coupled with a positive cerebrospinal fluid (CSF) JC virus PCR is sufficient for the unequivocal diagnosis of PML³.

This paper describes an unusual case of PML in a patient with follicular non-Hodgkin lymphoma following treatment with rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovicin and prednisolone (R-CHOP regimen).

Case Report

A 54-year-old woman was diagnosed in May 2012 with a follicular non-Hodgkin lymphoma

Figure 3 MRI obtained on admission (February 2014). Axial FLAIR showed multiple hyperintense lesions of the subcortical and deep white matter, symmetrically involving the cerebral hemispheres and cerebellum. The lesions were round or ovoid without significant mass effect, did not conform to cerebrovascular territories and were consistent with PML.

Figure 4 MRI obtained on admission (February 2014). On T1-weighted sequences obtained after administration of gadolinium, the lesions did not show enhancement.

grade 1, stage 3A, FLIPI (Follicular Lymphoma International Prognostic Index) score 2. She was treated with the R-CHOP regimen (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovicin, prednisolone) from July to November 2012; she tolerated the treatment well and achieved a complete response. Thereafter, she was treated with rituximab alone from March to December 2013. The patient had a whole body PET-CT scan in September 2013 that did not reveal any signs of recurrent or systemic disease.

In December 2013, she noticed gradually progressive neurological symptoms, such as headache, memory loss (short and long-term), slurred speech, gait disturbance, confusion and disorientation. Her relatives reported that she appeared confused and took longer than usual to respond to their questions or suggestions. In January 2014, she had a brain MRI that resulted negative (Figure 1). Her neurological symptoms continued to worsen and she eventually developed a myoclonic seizure. In February

Figure 5 MRI obtained on admission (February 2014). The proton MR spectrum demonstrated a mild elevation of the choline (Cho) peak, with an increased Cho/Cr ratio, and a slightly decreased N-acetyl aspartate peak, with a mildly reduced NAA/Cr ratio. There were also a mild elevation of mI (myo-inositol) and two abnormal peaks at 0.9 ppm and, greater, at 1.3 ppm, due to the presence of lactate and lipids, with an increased lac/Cr and lipids/Cr ratio.

Figure 6 Follow-MRI obtained two months after hospital admission (April 2014). Axial FLAIR at almost the same levels as Figure 3 showed an increase in the number and width of the lesions.

2014, she was admitted to our Neurology Department due to her history of progressive cognitive impairment. On admission, she was not awake but responded to strong verbal stimuli. Thereafter, she had bowel and bladder incontinence, psychomotor slowing, myoclonic seizure, diffuse muscle weakness. She could not walk unassisted, had a positive Romberg test

but a negative Babinski response. Gait testing revealed ataxia. She was found to be afebrile and the vital signs were normal. Breath sounds were clear and oxygen saturation was normal. Her medications included acetylsalicylic acid, bisoprolol, telmisartan and atorvastatin.

Laboratory investigations were significant for a low lymphocyte count of 13% (normal range

20-43%) and a low serum immunoglobulin (Ig) concentration of 620 mg/dL (normal 800-1350 mg/dL). Laboratory tests also showed a normal haemoglobin level, white blood cell and neutrophil counts. Electrolyte levels, renal function panel results, cardiac and liver enzyme levels were in range. Electroencephalography (EEG) was characterized by a slow background activity with triphasic waves (Tws) and slow waves predominantly in the frontal regions.

The patient was admitted to Department of Radiology for a brain CT that showed multiple hypodense lesions in the white matter of the cerebral and cerebellar hemispheres (Figure 2). She had also a brain MRI that compared with the previous MRI showed widespread lesions of the subcortical and deep white matter consistent with a demyelinating process. The cerebral hemispheres and cerebellum were involved in a symmetric way. The cortex, basal ganglia and the thalami were spared. T2-weighted and fluid-attenuated inversion recovery (FLAIR) MR images showed multiple scattered hyperintense focal lesions in the subcortical, deep and periventricular white matter of the fronto-parieto-occipital region bilaterally and in the cerebellum (Figure 3). The lesions were round or ovoid, without significant mass effect and did not conform to cerebrovascular territories. Restricted diffusion was not noted. On T1-weighted sequences, the lesions showed a decreased signal. No enhancement was observed following administration of gadolinium (Figure 4).

Investigation with MR spectroscopy showed a mild reduction of the N-acetyl aspartate (NAA) peak, with decreased NAA/Cr ratio, and a slightly elevated choline (CHO) peak, with increased Cho/Cr ratio. There was also a mild elevation of the mI (myo-inositol) peak and two abnormal peaks at 1.3 ppm and smaller at 0.9 ppm, due to the presence of lactate/ lipids, with increased lac/Cr and lipids/Cr ratios (Figure 5).

The main differential diagnoses were CNS involvement by lymphoma cells and PML. Absence of mass effect and contrast enhancement were important distinguishing features and PML was suspected. In addition, whole body PET-CT scan showed no areas of hypermetabolic activity to suggest relapsed lymphoma.

Her serology was negative for human immunodeficiency virus (HIV), hepatitis B and hepatitis C.

A lumbar puncture for CSF was held. The CSF had an increased protein level of 57.2 mg/dl (normal 15-45 mg/dl), an increased albumin level of 43.2 mg/dl (normal 0-35 mg/dl) and a

high IgG level of 4.73 mg/dl (normal 0-4 mg/dl). There was a high CSF/albumin ratio of 13 (normal <9). The total cell count in the CSF was normal, with normal levels of glucose and a negative Gram stain. Herpes simplex virus DNA was not detected in the patient's CSF by the polymerase chain reaction (PCR).

PCR of the CSF and serum showed JCV DNA and so PML was diagnosed.

During her hospital admission, the patient received medical treatment, including levetiracetam and mirtazapine, but reported a progressive worsening of the clinical and radiological findings (Figure 6).

Discussion

Progressive multifocal leukoencephalopathy (PML) was first described by Astrom, Mancall and Richardson in 1958⁵. PML is an uncommon demyelinating disease of the CNS characterized by the destruction of oligodendrocytes due to the reactivation of a type of human polyoma virus called the John Cunningham (JC) virus⁶, a double-stranded DNA virus named after the individual from whom the virus was first isolated⁷. It has a rapid clinical course with an extremely poor clinical outcome, the overall median survival without treatment being a mere 3.5 months⁶. Nearly all patients who survive suffer from residual neurologic deficits including hemiparesis, motor aphasia and visual defects⁶.

The target cells for JC virus are oligodendrocytes, although both glial cells and astrocytes express the receptor for JC virus (5-hydroxytryptamine receptor 2A)⁶. Astrocytes and oligodendrocytes support JCV replication and thus JCV accumulates to high concentrations in oligodendrocytes causing their destruction by cytolysis and resulting in neurological deficits¹. PML is characterized by disseminated demyelinating plaques in the cerebral white matter and adjacent areas¹ without perivenular inflammation, characterized by oligodendrocytes with enlarged nuclei, inclusions and bizarre astrocytes⁸. Demyelination may, on rare occasions, be monofocal, but it typically occurs as a multifocal process, suggesting a haematologic spread of the virus¹. These lesions may occur in any location in the white matter and range in size from one millimetre to several centimetres; larger lesions are not infrequently the result of coalescence of multiple smaller lesions¹. The myelin loss may be very extensive, in-

volving an entire hemisphere, and may result in atrophy of the affected structures¹.

JC virus is a ubiquitous virus: 70-80% of the adult population has been infected and seroconversion rates to JCV exceed 90% in some urban areas⁵. Furthermore, up to 64% of healthy adults have shedding of JC virus in urine in the absence of any clinical symptoms, suggesting that asymptomatic active JC virus infection is common in immunocompetent persons⁹. Reactivation of the virus occurs almost exclusively in patients with an impaired cellular immune response: 80/85% of reported PML patients have AIDS, 13% have haematologic malignancies, 5% are transplant recipients and 2% have chronic inflammatory diseases^{6,10}.

The exact pathogenesis is still unclear but the primary infection is thought to occur in childhood through the respiratory and gastrointestinal tracts without apparent illness⁸.

Bofill-Mas and Girones have proposed contaminated food and water as potential sources of infection⁵. After the primary infection, the virus remains latent in the kidney, bone marrow and lymphoid organs, but, in a setting of cellular immunosuppression, the JC virus reactivates, spreading to the CNS⁴.

The site and modality of JCV reactivation are still poorly understood but the most likely hypothesis is that the virus reactivates somewhere in the periphery, where it infects circulating cells such as B lymphocytes, and through these cells crosses the blood-brain barrier entering the CNS where it infects astrocytes².

Treatment with monoclonal antibody products is a unique, newly identified predisposing factor for the development of PML⁵. Among the monoclonal antibodies that increase the risk of PML are natalizumab (Tysabri®), efalizumab (Raptiva®) and rituximab (Rituxan®)⁵. At present, more than 70 cases of PML have been associated with the use of rituximab, predominantly in patients treated with lymphoproliferative disorders, very rarely during treatment with the R-CHOP regimen¹¹.

Rituximab is a chimeric human / mouse IgG1 monoclonal antibody that targets the CD20 antigen expressed on the surface of both normal and malignant B lymphocytes⁶. While being expressed in nearly 90% of B-cell non-Hodgkin lymphomas (NHLs) and a smaller proportion of B-cell chronic lymphocytic leukaemia (CLL) cells, the CD20 antigen is not expressed by haematopoietic stem cells⁶. CD20 is expressed by pre-B and B-cells, by all mature peripheral blood cells but not by resting or activated T

cells, monocytes or granulocytes^{5,12}. As a result, treatment with rituximab is associated with an initial severe decrease in mature B lymphocyte count which recovers nine to 12 months following completion of therapy⁶. The reduction of mature B cells determines pre-B cell release into the circulation to repopulate B-cell functions. If these cells are latently infected with JCV, detectable virus may be observed in the peripheral blood⁵. These lymphocytes carry the virus to the CNS where it infects and destroys oligodendrocytes⁵. Therefore, PML following rituximab therapy develops in conjunction with the reconstitution of the B-cell population⁵, as in our patient who presented clinical symptoms two months after completion of rituximab treatment. The mechanism underlying viral reactivation after rituximab treatment is probably more complex than simple B-cell depletion^{2,13}. Additionally, rituximab may also have reduced CD3 T-cells in the CSF⁵.

Rituximab was approved in the USA in 1997 for the treatment of NHL and is currently approved for the treatment of CD20-positive haematologic malignancies (NHLs and CLL) and as maintenance therapy for follicular lymphoma and other indolent B-cell malignancies⁶. Rituximab has also been employed for the treatment of non-malignant autoimmune disorders, chiefly rheumatoid arthritis and systemic lupus erythematosus (SLE)⁶, and even for multiple sclerosis and neuromyelitis optica⁵.

In 2006, following the report of two patients with SLE who developed PML after rituximab treatment, the Food and Drug Administration issued an alert concerning the use of rituximab in SLE⁶. The risk quantification of PML related to the use of rituximab is difficult because PML has been described in SLE, rheumatoid arthritis, lymphoma and leukaemia independently from the use of any treatment¹⁴. In the general population, PML is estimated to occur in one case per 200 000 persons¹⁰. Carson et al.¹⁵ reviewed 57 cases reported during the years 1997-2008. In a retrospective review of rituximab-treated non-Hodgkin lymphoma patients, Tuccori et al.¹⁶ found an incidence rate of 0.1-4.3 /1.000 patient years. This rate exceeds those observed in patients with HIV infection or B-cell chronic lymphocytic leukaemia, traditionally considered at highest risk of PML¹⁷. However, this study could be affected by limitations, resulting in a possible overestimation of the PML risk¹⁶. Rituximab administration may increase the risks of developing PML, although the absolute risk of developing

PML is probably low¹⁰ and does not overcome the benefits in terms of mortality exerted by rituximab in most NHL patients¹⁶. As use of rituximab expands to diverse clinical settings, clinicians and patients should be aware of the potential for PML after rituximab therapy¹⁰.

The disease appears to set in relatively early in affected patients following the start of rituximab therapy (median time of onset from the last dose being about six months), progresses rapidly (median time to death following diagnosis about two months) and is nearly always fatal⁶. Factors predicting a rapid progression of the disease include a CD4+ lymphocyte count <500 cells/ μ l and diagnosis of PML within three months following the start of rituximab therapy⁶.

A definitive diagnosis of PML can be based on the concomitant presence of clinical neurological findings, neuroimaging findings, JC virus-positive PCR in the CSF and brain biopsy¹. However, brain biopsy is an invasive method with considerable risks¹. PML is multisymptomatic presenting with a wide clinical spectrum⁸. Neurological symptoms and signs may be focal or diffuse and may include motor deficits, visual symptoms, altered consciousness, gait and ataxia². Some studies have developed and validated less invasive diagnostic methods based on the detection of the virus in CSF by PCR¹. Fong et al. showed that the sensitivity and specificity of JCV DNA by PCR were 74 and 96%, respectively, and the positive and negative predictive values were 89.5 and 88.5%^{1,15}.

In the appropriate clinical context, brain imaging may strongly support the diagnosis of PML³. CT reveals hypodense lesions in the affected white matter, which exhibit no mass effect and infrequently contrast enhance³. A "scalloped" appearance beneath the cortex is noted when the subcortical arcuate fibres are involved³.

MRI is far more sensitive than CT and MRI FLAIR images are the most sensitive in detecting the lesions of PML, even in the posterior fossa³. The MRI findings in patients with PML present characteristic images¹. MRI shows hyperintense lesions on T2-weighted images and FLAIR images³, which are hypointense on T1-weighted images³. This is reflected by a slight tissue swelling in acute lesions and atrophy in end-stage areas during the demyelination process¹. Most lesions remain hyperintense on T2-weighted images because the tissue water content increases after the replacement of oligo-

dendrocytes by astrocytes¹. Tissue destruction continues in clinically progressive patients¹, as in our case.

The lesions of PML may occur virtually anywhere in the brain and although characteristically multifocal, they need not be³. The typical lesions involve the subcortical white matter of the cerebral hemispheres and cerebellar peduncles³. In every radiographic series of PML, the frontal lobes and parieto-occipital areas are the regions that appear to be most commonly affected, presumably as a consequence of their volume³. However, isolated or associated involvement of the basal ganglia, external capsule and posterior fossa structures (cerebellum and brainstem) may be seen as well³.

Generally, the lesions in PML are not contrast-enhanced by gadolinium and do not show a substantial mass effect¹. DWI reliably distinguishes intracellular oedema from interstitial water accumulation¹. Intracellular oedema is seen in acute cell damage, which is usually followed by cell death¹. Cell death as observed in the periphery of the cerebral lesions is explained as oligodendrocyte necrosis in the areas of demyelination^{1,12}.

Cross-sectional studies have shown a typical ¹H-MRS pattern in PML lesions, including a decreased NAA/Cr ratio consistent with axonal compromise, increased Cho/Cr ratio, indicating cell membrane breakdown and turnover, and occasional elevation of lipid/lactate and mI^{18,19}. The elevation of lipids is due to excess soluble lipids that are breakdown products of demyelination; the lactate peak is most likely due to the presence of necrotic oligodendrocytes and foamy macrophages¹⁹. In some studies, the patients who had the longest survival showed the highest mI, consistent with increased glial activity and hence with a more active repair process in PML lesions^{18,19}.

To date, there is no established therapy for PML⁸ and the treatment is mostly supportive⁶. In cases associated with immunomodulatory agents, the withdrawal of the drug and further elimination by plasma exchange is the most important therapy for immune system recovery⁸. There is evidence that JCV infects the cells through the α 5-HT_{2A} serotonin receptor⁴. Mirtazapine, an antidepressant that acts by inhibiting this receptor has been used in treatment of PML⁴, as in our patient. Although the concept sounds attractive and the drug is usually well-tolerated, the benefit is modest, the evidence to date is scarce and based mostly in case reports and small series⁴. Although PML

has a poor prognosis, prompt diagnosis and treatment allow an attempt to slow disease progression as much as possible.

Conclusions

The present case report describes a rare but deadly complication of rituximab therapy. In cases with a relatively rapid progressive neu-

rological disorder affecting the entire nervous system and mainly involving the white matter, it is important to consider PML to obtain an early diagnosis. Furthermore, in patients treated with rituximab is extremely important to evaluate any new neurological symptoms in order to make an early diagnosis and monitor them with MRI. Furthermore, it is important to educate physicians who prescribe rituximab and patients who receive the drug about PML.

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