Rituximab-Associated Progressive Multifocal Leukoencephalopathy in Rheumatoid Arthritis

Objective: To describe the development of progressive multifocal leukoencephalopathy (PML) in patients with rheumatoid arthritis (RA) treated with rituximab.

Design: Case study.

Setting: Clinical care for patients with rheumatologic diseases. Most were referred to academic centers for care after diagnosis (Washington University, St Louis, Missouri; Karolinska Institute, Stockholm, Sweden; and Royal Melbourne Hospital, Melbourne, Australia) while one was cared for in a neurology practice in Dallas, Texas, with consultation by an academic neurovirologist from the University of Colorado in Denver.

Patients: Four patients developing PML in the setting of rituximab therapy for RA.

Intervention: Rituximab therapy.

Main Outcome Measures: Clinical and pathological observations.

Results: Four patients from an estimated population of 129,000 exposed to rituximab therapy for RA are reported in whom PML developed after administration of this drug. All were women older than 50 years, commonly with Sjogren syndrome and a history of treatment for joint disease ranging from 3 to 14 years. One case had no prior biologic and minimal immunosuppressive therapy. Progressive multifocal leukoencephalopathy presented as a progressive neurological disorder, with diagnosis confirmed by detection of JC virus DNA in the cerebrospinal fluid or brain biopsy specimen. Two patients died in less than 1 year from PML diagnosis, while 2 remain alive after treatment withdrawal. Magnetic resonance scans and tissue evaluation confirmed the frequent development of inflammatory PML during the course of the disease.

Conclusion: These cases suggest an increased risk, about 1 case per 25,000 individuals, of PML in patients with RA being treated with rituximab. Inflammatory PML may occur in this setting even while CD20 counts remain low.

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Rituximab, a chimeric monoclonal anti-CD20, is one of the most widely used monoclonal antibody drugs. It is widely used in the treatment of lymphoproliferative diseases such as chronic lymphocytic leukemia and CD20+ non-Hodgkin’s lymphoma. A recent report found 57 cases of PML associated with rituximab use in HIV-negative patients. Unlike the situation with multiple sclerosis or psoriasis, many of the underlying diseases for which rituximab therapy was used had previously been associated with PML, with more than 90% of cases with complicating lymphoproliferative conditions. Determining any increased risk of PML attributable to rituximab is confounded by the uncertainties about the number of exposed patients, the use by most patients of multiple immunosuppressive drugs, and the lack of reliable incidence data for PML in lymphoproliferative and rheumatological diseases in the absence of rituximab therapy. A Food and Drug Administration alert concerning 2 cases of PML associated with rituximab use in systemic lupus erythematosus drew further attention to this problem (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126519.htm). Reviews by Calabrese and Molloy have focused on PML risk in rheumatic disease, finding a somewhat higher risk in systemic lupus erythematosus than other settings such as rheumatoid arthritis (RA).

Until very recently, treatment of RA with rituximab had not been associated with development of PML. However, recently, a patient with RA who had been treated with rituximab and developed PML was reported. In this previously reported case, attribution of risk for PML was complicated by a history of malignancy that had been treated with chemotherapy and irradiation a short time before PML onset. Herein, we report the clinical and pathological results from 4 additional cases of PML that developed in the context of treatment for RA using rituximab. Our results suggest that exposure to rituximab leads to an increased risk of PML.

### METHODS

Patients presented with clinical signs of possible PML that were further worked up at each of the contributing institutions. Each of the cases was reported to Genentech, the company that markets rituximab. Clinical data were compiled with the assistance of treating physicians.

### RESULTS

Table 1 provides a summary of demographics of the 4 new cases of rituximab-associated PML in HIV-negative
patients with underlying RA that we have collected, as well as the previously reported information from the original case. \(^{18}\) In each, symptomatic PML was confirmed by either biopsy or cerebral spinal fluid detection of JC virus subsequent to treatment with rituximab. All of the patients were women, with the median age of patients being 67 years (range, 51-73 years). All patients had been diagnosed with moderate to severe RA with disease duration of at least 3 years. Currently, rituximab is not considered a first line of therapy for patients with RA, so treatment with this drug was started in each patient only after failure of other interventions, including methotrexate, other biologics, or corticosteroids. In each case, the rituximab was administered at the recommended dose for refractory RA of two 1000-mg infusions at a 2-week interval for each course. Two patients received only 1 course. The maximal number of courses was 5 (case 4), where the final dose was given between clinical presentation and diagnosis or PML. All patients were negative for HIV. Two may have had enhanced risk due to cancer, 1 having breast cancer treated with surgery and chemotherapy, while another (previously reported\(^{18}\)) developed superficial squamous cell carcinoma of the oropharynx with chemotherapy and irradiation after rituximab therapy and before diagnosis or PML. All patients were negative for HIV. Two patients received only 1 course. The maximal number of courses was 5 (case 4), where the final dose was given between clinical presentation and diagnosis or PML. All patients were negative for HIV. Two may have had enhanced risk due to cancer, 1 having breast cancer treated with surgery and chemotherapy, while another (previously reported\(^{18}\)) developed superficial squamous cell carcinoma of the oropharynx with chemotherapy and irradiation after rituximab therapy and before diagnosis or PML. Lymphopenia was reported in 4 of 5 cases, but comprehensive testing of immune competence was not routinely available.

The clinical, laboratory, and radiological findings of PML for each case are summarized in Table 2. Onset of symptoms in 3 cases occurred 5 to 7 months subsequent to treatment with rituximab. All of the final dose was given between clinical presentation and diagnosis or PML.

### Table 2. Features of Rituximab-Associated PML

<table>
<thead>
<tr>
<th>Feature</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (From Fleischmann(^{18}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval from rituximab infusion to PML onset, mo</td>
<td>5</td>
<td>7</td>
<td>16</td>
<td>5 (after 3rd of 4 cycles)</td>
<td>18 (CD20 count recovery to 7 mo, then chemotherapy for cancer, then recovery and onset of PML)</td>
</tr>
<tr>
<td>Presenting symptom/sign</td>
<td>Focal R-hand dysesthesia; ataxia/dysphasia</td>
<td>Right hemiataxia in arm, leg, and trunk, with falls</td>
<td>Cognitive decline, dysphasia</td>
<td>Cortical R-hand dystonic tremor, evolved to segmental myoclonus (unresponsive to valproate sodium and levetiracetam; some improvement with clonazepam)</td>
<td>Inability to walk (in setting of malnutrition, pneumonia)</td>
</tr>
<tr>
<td>MRI at baseline</td>
<td>Multiple WM lesions, no enhancement, DWI bright at onset</td>
<td>Multiple punctate WM lesions, atrophy</td>
<td>L gyrus frontalis white matter lesion (Sep 2009)</td>
<td>L precentral gyrus lesion, small T2 hyperintense/T1 hypointense lesion</td>
<td>Multifocal WM lesions, R frontal predominant</td>
</tr>
<tr>
<td>CSF JC viral load, copies/mL, baseline</td>
<td>Undetectable initially, detected 1 mo late</td>
<td>JC virus DNA detected, 9138 copies at NIH 4 mo after symptoms by history</td>
<td>JC virus DNA not detected Sep 2009; 280 copies/mL, JC virus DNA Nov 2009</td>
<td>Not detected; brain biopsy for diagnosis</td>
<td>None</td>
</tr>
<tr>
<td>Therapy used</td>
<td>Mefloquine</td>
<td>Mirtazapine, up to 45 mg/d; mefloquine Dec 2008 onward</td>
<td>Mirtazapine, 30 mg/d; mefloquine; and prednisolone Jan 2010 Nov 2009 to Feb 2010</td>
<td>Mefloquine; mirtazapine; plasma exchange</td>
<td>None</td>
</tr>
<tr>
<td>MRI evolution</td>
<td>Lesions increasing in size and number over weeks; late contrast enhancement</td>
<td>New T2/FLAIR lesion in pons/peduncle Dec 2008, no enhancement (4 mo after last infusion), further progression Mar 2009</td>
<td>New parietal and occipital lesions, enlargement, Gd enhancement at 5 mo</td>
<td>New parietal and occipital lesions, enlargement, Gd enhancement at 5 mo</td>
<td>Progression in weeks, extension in L hemisphere, as well as R hemisphere lesions (no contrast mentioned)</td>
</tr>
<tr>
<td>CSF JC viral load evolution</td>
<td>Increased to 47 000, then declined to 1859 copies/mL</td>
<td>Declined to 684</td>
<td>Declined while scan worsened (not detected)</td>
<td>Not detected in CSF (biopsy diagnosis)</td>
<td>None</td>
</tr>
<tr>
<td>Evidence of IRIS</td>
<td>Developing Gd contrast on MRI, spikes/seizures?; MRI DWI</td>
<td>None</td>
<td>Worsened scan, developed contrast enhancement, CD19 counts approaching normal range during IRIS</td>
<td>Evolved enhancement and contrast enhancement 2 mo after diagnosis, mass effect developed, mass and contrast improved after 10 mo</td>
<td>Inflammatory changes on biopsy specimen; rapid progression to death in weeks with no steroid treatment</td>
</tr>
<tr>
<td>Course/outcome</td>
<td>Spasms, progression to death</td>
<td>Progression, brainstem/cerebellar findings, progressive disability to death 11 mo from first symptoms</td>
<td>Alive without progression of neurological symptoms</td>
<td>Alive without progression of neurological symptoms</td>
<td>Progressed to death in 4 wk</td>
</tr>
<tr>
<td>Histological features</td>
<td>Inflammatory PML; abundant JC virus DNA on immunostain; perivascular inflammatory response; CD8 cells abundant; CD20 cells present in the brain</td>
<td>NA</td>
<td>NA</td>
<td>Biopsy had no CD20 cells at diagnosis, CD4 &gt;&gt; CD8 count, patient survived, typical PML histological features with demonstration of virus with histochemical and electron microscopic analysis</td>
<td>Biopsy at diagnosis: inflammatory changes with T/B/plasma cells, macrophages, gliosis</td>
</tr>
</tbody>
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Abbreviations: CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium; IRIS, immune reconstitution inflammatory syndrome; L, left; MRI, magnetic resonance imaging; NA, not available; NIH, National Institutes of Health; PML, progressive multifocal leukoencephalopathy; R, right; WM, white matter.
In case 1, MR scans with pathologic correlation show consistent with unrelated preexisting vascular disease. The lesion in case 2 was poorly visible early, but a positive brain biopsy diagnosis of PML. This patient, a rituximab dose had been given after onset of symptoms later attributed to PML, so PLEX was tried since this drug has a long half-life. The abrupt augmentation of lesions on MR imaging between the September 2009 and November 2009 scans is consistent with development of inflammation in the lesions following PLEX. Survival in this case is also consistent with an effective inflammatory control of PML after withdrawal of immunosuppression.

Figure 1. Magnetic resonance imaging of progressive multifocal leukoencephalopathy lesions from cases 1 to 4. A, Case 1 T2 fluid-attenuated inversion recovery (FLAIR) brain image demonstrating predominant left parietal lesion (arrow) in the setting of many presumed vascular lesions that had been seen on a previous scan a year prior to onset of progressive multifocal leukoencephalopathy symptoms and signs. B, T2 FLAIR image from case 2, who developed a right cerebellar lesion (arrow) radiating into the brainstem that was not visible at the onset of disease but was seen here at 8 months after clinical concerns began. C, Case 3 presented with left frontal white matter disease seen on this T2 magnetic resonance image (arrows). D, T2 FLAIR image from case 4. The patient presented with a small left posterior parietal subcortical white matter lesion (arrow) that subsequently progressed markedly (see Figure 3).

Figure 2. Magnetic resonance characteristics of a progressive multifocal leukoencephalopathy lesion. A-D, Apparent diffusion coefficient (ADC) (A) and diffusion-weighted (B) imaging with the pathologic correlates at post mortem (C and D). Note the inverse relationship of the gliotic lesion where ADC is bright (arrowhead) (A) contrasted with the necrotic core bright on the diffusion-weighted image (arrowhead) (B) and seen at the arrowhead in part C. The active rim of the lesion where viral replication is inducing cytotoxic edema and swelling of oligodendrocytes is highlighted in the ADC image (A). Whole-mount image immunostained for CD68, a marker of macrophages, shows the necrotic core lesion (arrowhead) and the rim of gliosis (arrow) (C) (original magnification ×1). CD68 microscopic image shows many macrophages from the rim of active disease (D) (original magnification ×40).

scans illustrate the reported presentation of PML with diffusion-weighted imaging bright lesions that may be confused with stroke. The development of edema and contrast enhancement typical of inflammatory PML was also seen repeatedly, typical of evolution of inflammatory PML in this setting. Figure 3 demonstrates serial MR scan images of case 4's developing and resolving IRIS after plasma exchange (PLEX) initiated following brain biopsy diagnosis of PML. In this patient, a rituximab dose had been given after onset of symptoms later attributed to PML, so PLEX was tried since this drug has a long half-life. The abrupt augmentation of lesions on MR imaging between the September 2009 and November 2009 scans is consistent with development of inflammation in the lesions following PLEX. Survival in this case is also consistent with an effective inflammatory control of PML after withdrawal of immunosuppression.

Diagnosis of PML was confirmed based on clinical presentation with progressive neurological deficits in all cases, laboratory study results including cerebrospinal fluid (CSF) JC viral levels or a positive brain biopsy specimen (case 4), and MR imaging lesions suspicious for PML. JC virus DNA was frequently not detected in the CSF at initial presentation and was found only after repeated lumbar punctures as the disease progressed. In fact, in case 4, results of CSF studies were repeatedly negative, making a brain biopsy necessary to confirm PML. The previously published case (case 5) also required a brain biopsy but CSF JC viral copy levels were never reported. With progression of the disease,
an increase in the number and/or size of MR imaging lesions occurred over time in all cases. Three cases developed MR gadolinium enhancement typical of IRIS, suggesting that this is often a complication of rituximab-associated PML. In all cases where CSF JC viral levels were detected, the loads declined over time, consistent with the experience from those with HIV-associated PML who survive.21,22 The outcome of this complication underscores the serious nature of this disease, with 60% dying while surviving patients typically have significant impairment. Three of the 5 cases had brain tissue examined, either post mortem or at biopsy. In 2 of the 3, notable inflammatory PML was documented. Immunohistochemical examination of brain tissue revealed the presence of many lymphocytes. In case 1, some CD20+ cells could be found in the postmortem brain, while no CD20+ cells were identified in the lesion from a diagnostic biopsy specimen from case 4 at an earlier time in the course of the PML. In all 3 cases, JC virus was confirmed in brain tissue (Figures 2, 4, and 5).

**COMMENT**

We document 4 additional cases of rituximab-associated PML occurring in the setting of underlying RA, extending the information available from the prior single published case report.18 Given the rarity of RA-associated PML, these cases support the hypothesis that rituximab increases the risk of PML in this setting. Rheumatoid arthritis has not been commonly associated with PML, although patients living with it commonly take other immunosuppressive drugs that have been associated with this condition.23 Calabrese and Molloy15-17 used the Nationwide Inpatient Sample data to document that the rate of PML in patients with RA is 0.4 per 100 000 discharges, compared with 0.2 for the general population (excluding acknowledged high-risk conditions of HIV, malignancy, and organ transplant) while another incidence study found no cases of RA-associated PML.23 With 5 described cases of rituximab-associated PML in patients with RA and an estimated 129 000 exposed (A. Kelman, MD, Genentech, Inc, written communication, May 20, 2010), incidence is probably at least 1 in 25 000 exposed patients, especially given that not all involved patients may have been accurately diagnosed or reported. While this evidence suggests that risk is increased, it is less than the apparent risk of PML with natalizumab treatment, which is about 1 in 1000 patients exposed for more than 24 months,10,11 or for efalizumab, where risk may have been as high as 1 in 400 exposed patients.24 Risk of PML associated with rituximab has been particularly difficult to characterize. While many cases of PML are reported,14 in most cases they have occurred in individuals with a well-known concomitant risk of PML. This factor, as well as the absence of a clear denominator for exposure, and probable missed cases of PML have made it challenging even for interested professionals collecting all available data to decide if any increased risk exists. To our knowledge, the present series of cases is the most decisive evidence available, documenting a growing number of cases in a setting where PML was very rare, including 1 case (case 1) where there were minimal other significant risks outside the recent exposure to rituximab.
This case series is instructive in an additional way, since PML in this setting differs from that seen in the case of malignancy or untreated HIV by the common occurrence of PML with IRIS. This factor is critical for clinicians, since it impacts diagnosis and management. Detection of JC virus DNA in CSF was insensitive for PML diagnosis early in the disease onset. This may reflect low copy numbers, a phenomenon recently reported in natalizumab-associated PML cases.\textsuperscript{11,25} If PML presents during IRIS, CSF viral loads are likely to be low or undetectable, making a brain biopsy necessary to confirm the diagnosis. If inflammatory changes are under way, the lesions may transform, accounting for the appearance of gadolinium enhancement, which is atypical for PML in other settings. This inflammatory component may exacerbate neurological signs and symptoms and cause a further decline in the patient’s status. Immune reconstitution inflammatory syndrome associated with PML can be a life-threatening complication requiring therapy such as corticosteroids to optimize survival and best functional outcomes.

The mechanism of increased risk of PML in association with rituximab remains unknown. The immune deficiency experience in AIDS, where the greatest risk for PML occurs, is typified by cellular immune deficiency with progressive loss of CD4 lymphocytes but with relative preservation of humoral immunity. Given the routine presence of antibody to JC virus when PML develops, and the important association of JC virus-specific CD8 cells to the prognosis for survival from PML, the humoral immune system has generally been thought to be of secondary importance in this disorder.\textsuperscript{26,27} Lymphopenia was chronic in 75% of our cases, providing a prolonged setting in which JC virus may have spread and transformed to enhance neurovirulence. Therapy that targets CD20 cells and the humoral immune system was thought theoretically to carry less risk for PML. Our cases suggest that optimal control of JC virus requires both intact B and T cells. An alternative possibility may be that B-cell precursors, believed to be a site of infection in the marrow, may be critical to activation and spread of the virus with subsequent risk of PML. Depletion and reconstitution of CD20 cells occurring during rituximab therapy may enhance the spread of virus from marrow to the brain. It is interesting that our cases appear to occur during immune reconstitution following rituximab therapy, rather than when CD20 cells are at their nadir.

It is now apparent that a modest increase in the risk of PML should be considered with the use of rituximab, and potentially other agents that target CD20 cells. Given the benefit that this drug provides many patients, it re-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Pathology of rituximab-associated progressive multifocal leukoencephalopathy. A, Case 1 demonstrating a large demyelinated and focally necrotic white matter lesion at autopsy, especially prominent at the arrow. B, Hematoxylin-eosin–stained section of the brain from case 1 showing marked perivascular inflammation consistent with immune reconstitution inflammatory syndrome in progressive multifocal leukoencephalopathy. The inset is a CD3 immunostain demonstrating the presence of T lymphocytes in both perivascular and parenchymal regions (original magnification ×100; inset, ×200). C, Histological analysis from the brain biopsy in case 4 demonstrating viral inclusions (arrows) and gliotic changes, with some perivascular inflammation (lower right inset), and the immunohistochemical detection of JC virus (upper right inset) (original magnification ×400; upper right inset, ×200; lower right inset, ×100). D, Electron micrograph from the brain biopsy specimen of case 4 demonstrating classic intranuclear papova viral particles, consistent with JC virus (original magnification ×100 000).}
\end{figure}
inforces the need to find means of detecting those at increased risk for this complication and ways to prevent its occurrence. In the case of natalizumab treatment, it has been suggested that patients who are JC virus seronegative prior to therapy are likely at reduced risk of developing PML, and a similar situation is likely to occur in the setting of rituximab treatment.3 Progressive multifocal leukoencephalopathy is presumed to result from reactivation of latent JC virus rather than from primary exposure. The presence of antibodies is indicative of past exposure to virus and probably identifies a higher-risk population. Conversely, the absence of antibodies likely indicates that primary infection with JC virus has not occurred and that risk of reactivation is therefore theoretically nonexistent.3,27

In the absence of prevention, early diagnosis of PML should be enhanced by clinical vigilance; education of practitioners, patients, and their families; and appropriate diagnostic efforts. Early discontinuation of therapy may allow for earlier immune reconstitution and improved outcomes. Effective direct antiviral treatment for the JC virus has not been demonstrated. An urgent need exists to find active drugs for treating PML. This includes both cytosine arabinoside28 and cidofovir,29 which are still occasionally tried in spite of significant evidence that they are not effective. Mefloquine hydrochloride was used in several of our cases and has in vitro activity against this virus. However, a recent clinical trial was stopped for lack of demonstrable efficacy.30 Similarly, clinicians continue to prescribe mirtazapine on a theoretical basis related to its potential efficacy in blocking serotonin receptors used for viral entry, despite absence for documented clinical efficacy.31

Assuming that rituximab contributes to PML in these cases, reversal of the drug’s effect would be appropriate. Plasma exchange has become a standard practice with natalizumab-associated PML.32 Rituximab is given infrequently in RA since CD20 counts remain depressed for 6 to 9 months after each treatment. While rituximab may remain detectable in plasma for 2 to 3 months, PLEX is unlikely to speed immune recovery after this period. However, if PML is discovered shortly after an infusion of rituximab, PLEX could be considered in this setting, as was performed in case 4 in our series. The apparent brisk increase in inflammatory changes of lesions following PLEX in this case and survival of the patient suggest the possibility this intervention may have been of benefit.

Immune reconstitution inflammatory syndrome, which occurred in our cases, provides an additional potential therapeutic avenue. While controlled trials are not available, the most commonly used treatment for inflammatory PML has been high-dose corticosteroid pulses, often 1 g of intravenous methylprednisolone daily for 5 days, which is repeated if symptoms respond and then recur. Steroid infusions have been reported to stop neurological decline in the setting of IRIS and initiate recovery, without evidence of increased risk.33 Physicians should

Figure 5. Immunohistochemical staining performed at autopsy of case 1. A, CD3 immunostain marks T cells, here demonstrating increased overall numbers as well as focal clumping around neurons (arrowhead), an atypical feature of progressive multifocal leukoencephalopathy that is more reminiscent of the neuronophagia encountered in cases of viral encephalitis (original magnification ×400). B, CD20 immunostain demonstrates B cells present in small numbers in the brain of the rituximab-treated patient (arrow) (original magnification ×200). C, CD68 immunostain shows numerous macrophages within an area of active demyelination (arrow) (original magnification ×200). D, JC virus immunohistochemical stain identifies numerous infected oligodendrocytes in the postmortem brain (arrow), even though rapidly declining JC viral loads were found in the blood prior to patient death (original magnification ×400).
Physicians considering the use of rituximab treatment of rheumatic diseases including RA should be aware that there is a potential, albeit modest risk of developing PML. Because of the morbidity and mortality of PML, however, it is important to consider this in the choice of treatments and to inform patients that this possibility must be considered with therapy including rituximab. In patients treated with rituximab, aggressive evaluation of new and progressing neurological deficits is very important to allow early diagnosis. No further rituximab should be used if a suspicious neurological symptom or sign appears until the diagnosis is successfully excluded.

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REFERENCES


Correction

Error in Byline and Affiliations. In the Reply Letter titled “How Safe Could Intrathecal Transplantation of Mesenchymal Stem Cells Be Considered in Multiple Sclerosis? In reply” by Karussis et al, published in the July issue of the Archives (2011;68[7]:955-956), a degree was missing from the byline and the affiliation was incorrect. Oded Abramsky, MD, should be Oded Abramsky, MD, PhD. Also, the affiliation for all authors should be The Center for Multiple Sclerosis and the Agnes Ginges Center for Human Neurogenetics, the Department of Neurology, Hadassah University Medical Center, Jerusalem, Israel.