

# Progressive multifocal leukoencephalopathy restricted to the posterior fossa in a patient with systemic lupus erythematosus

## ABSTRACT

Progressive multifocal leukoencephalopathy is a neurological infectious disease caused by the John Cunningham polyomavirus (JCV), an opportunistic agent with worldwide distribution. This disease is frequently seen in immunosuppressed patients and rarely associated with systemic lupus erythematosus. In the central nervous system PML demyelinating lesions occur in the supratentorial compartment. The authors describe a rare case of PML secondary to SLE treatment with atypical presentation restricted to the posterior fossa.

**Keywords:** PML; leukoencephalopathy; progressive multifocal posterior fossa; magnetic resonance; spectroscopy; diffusion weighted images.

## INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a neurological infectious disease caused by the John Cunningham polyomavirus (JCV),<sup>1,2</sup> an opportunistic agent with worldwide distribution. JCV is known to be indolent virus with very low viral replication rate in the vast majority of the hosts. In immunosuppression states, the virus can become reactivated which leads to oligodendrocytes destruction and demyelination.<sup>3</sup> PML is frequently seen in patients with acquired immune deficiency syndrome (AIDS), lymphoproliferative diseases, stem cell transplantation, in patients receiving monoclonal antibodies as treatment<sup>4</sup> and also in rheumatologic disorders. PML rarely occurs during the immunosuppressive treatment of systemic lupus erythematosus (SLE).<sup>5</sup> The authors describe a rare case of PML secondary to SLE treatment with an unusual location.

## CASE REPORT

A 52-year-old female was admitted to our hospital with progressive history of nausea, vomiting and recent gait instability. Past medical history was significant for SLE for more than 25 years. The patient had cardiac and skin SLE involvement, receiving 400 mg of hydroxychloroquine daily and mycophenolate mofetil

500 mg daily for SLE treatment. She was admitted the same day. On exam she presented spontaneous nystagmus, transient diplopia, right arm dysmetria, ataxia, uncoordinated walking and gait ataxia. Additionally, she also presented reduced control of range of movement of the arms, moderate hypotonia and mild tremor.

The laboratory investigation demonstrated inactive SLE status. She had negative screen for human immunodeficiency virus (HIV), VDRL, aspergillosis and hepatitis B. The cerebrospinal fluid (CSF) analysis was normal for cell count, protein and glucose. The work-up for coagulopathy was negative. The levels of vitamin B12 and folate levels were within normal limits.

The computed tomography (CT) scan has shown an area of hypodensity in the left middle cerebellar peduncle, also involving the left side of the pons and the deep white matter of the left cerebellar hemisphere (Figure 1). Magnetic resonance imaging was subsequently performed and revealed isolated lesions in the posterior fossa. The lesion in the right cerebellar peduncle extending to the right cerebellar hemisphere was hypo on the T1WI and hyperintense on the T2W/FLAIR images (Figures 2 and 3). No mass effect or significant enhancement were noted. The diffusion weighted images (DWI) revealed a slight peripheral rim of restricted diffusion (Figure 4).

## Authors

Fabício Guimarães Gonçalves<sup>1</sup>  
Leslie Lamb<sup>2</sup>  
Raquel Del Carpio-O'Donovan<sup>3</sup>

<sup>1</sup>Physician, Radiologist  
Clinical Fellow in  
Neuroradiology, McGill  
University Health Center  
Montreal General Hospital,  
Canada

<sup>2</sup>MD, MSc, Radiology  
Resident, McGill University  
Health Center Montreal  
General Hospital, Canada

<sup>3</sup>Professor of Radiology;  
Associate Director,  
Radiology MUHC Vice  
Chairman, Radiology  
McGill University Director  
Neuroradiology Fellowship  
Program, McGill University  
Health Center Montreal  
General Hospital, Canada

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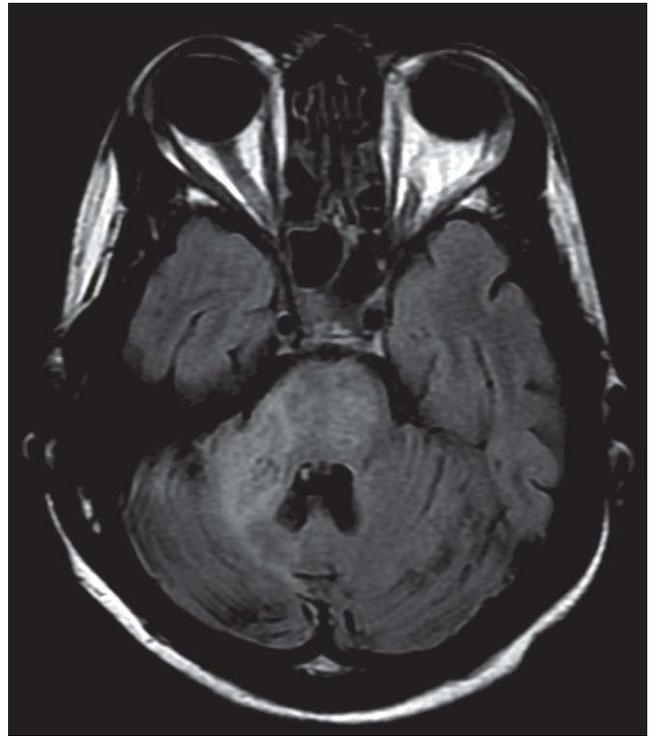
**Correspondence to:**  
Fabício Guimarães  
Gonçalves  
Diagnostic Radiology  
Montreal General  
Hospital  
1650 Cedar Avenue,  
Room C5 118  
QC H3G 1A4  
Montreal, Canada  
Phone: 514 934-8084  
Fax: 514 934-8263  
goncalves.neuroradio@  
gmail.com

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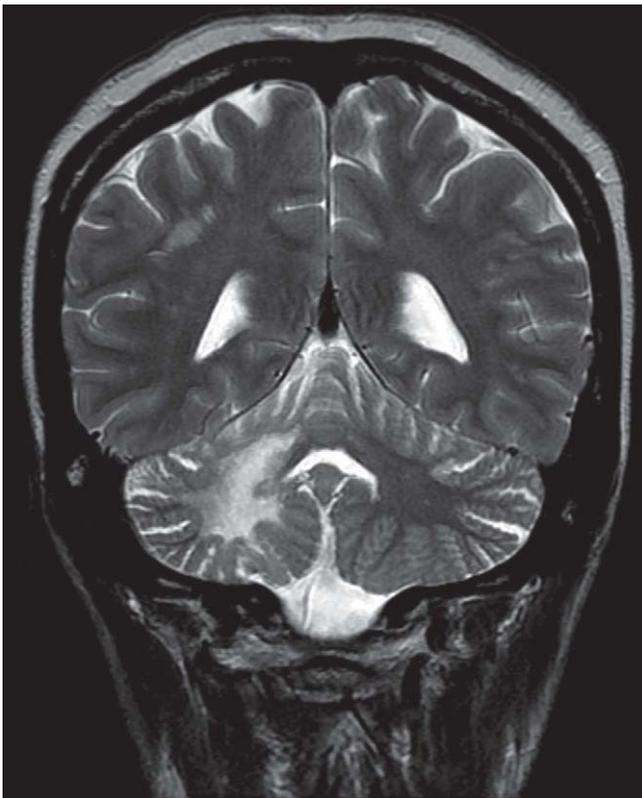
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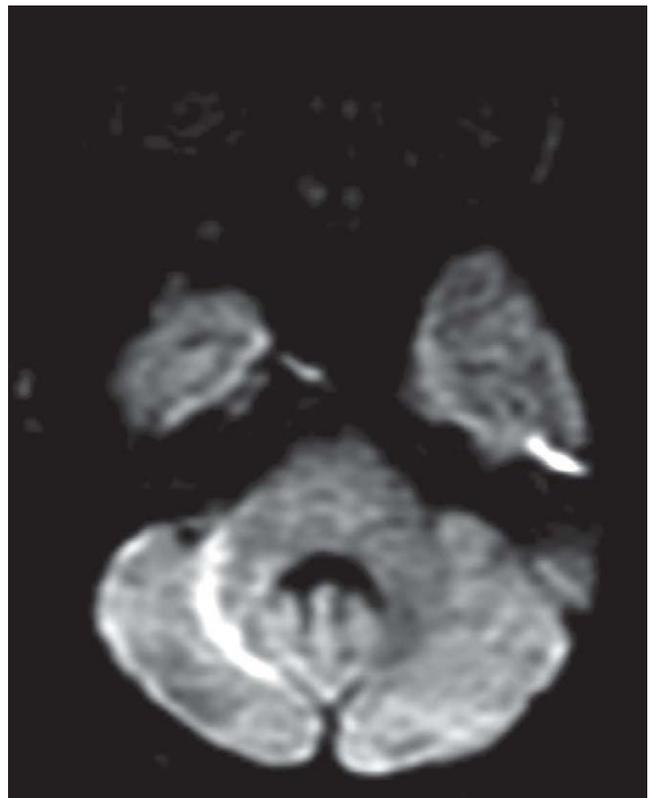
**Figure 1:** Plain CT of the brain in the axial plane demonstrates an isolated hypodense lesion in the left middle cerebellar peduncle extending anteriorly to involve the left side of the pons and posteriorly the deep white matter of the left cerebellar hemisphere.



**Figure 3:** Note the extensive white matter signal changes in the pons, right cerebellar peduncle and hemisphere with dismal mass effect, a typical feature of PML.



**Figure 2:** Coronal T2WI demonstrates the demyelinating lesion in the deep portions of the right cerebellar hemisphere involving the subcortical white matter and also encompassing the dentate nucleus.



**Figure 4:** Axial DWI image at the level of the posterior fossa demonstrating a curvilinear hyperintensity located at the margins of the demyelinating lesion. DWI hyperintensities in PML are associated with disease activity.

Vasculitic changes secondary to SLE was on top on our differential diagnosis list in such clinical scenario, followed by PML. All the vasculitis work-up was negative, including a normal conventional cerebral angiogram. CSF analysis was repeated, this time to perform a JCV CSF polymerase chain reaction (PCR), since biopsy of the brain was precluded. The PCR testing for JCV was positive and the patient subsequently started on cidofovir.

At the fourteenth day of admission, the patient became severely dysphagic and dysarthric. She also had acute pulmonary embolism and aspiration pneumonia. After seven days, the patient passed away of pulmonary insufficiency.

## DISCUSSION

PML is a rare, subacute, progressive and usually fatal disease of the central nervous system (CNS). The disease is characterized by widespread demyelinating lesions due oligodendrocytes infection by the JCV. The main histopathologic features of PML are: demyelination, enlarged nuclei of oligodendrocytes, and bizarre astrocytes.<sup>6</sup> It has been suggested that more than 90% of the general population present antibodies to the virus but less than 10% will show any evidence of viral replication. Isolation of the JCV in brain tissue confirms the diagnosis of PML. JCV CSF PCR has also been proved useful in the diagnosis of PML.<sup>6,7</sup> Typically the patients with PML present with cognitive impairment, altered mental status, aphasia, focal motor deficits, cortical blindness and behavioral changes.<sup>8,9</sup>

PML is predominately seen in cases of impaired cell-mediated immune response, almost exclusively in patients with AIDS.<sup>8</sup> Around 5% of these patients will develop PML, particularly when the CD4 counts are in the range of 50-100 cells. Prior to the AIDS epidemic, PML was rarely seen in other immunocompromised patients occurring usually as a terminal event such as in cases of leukemia, lymphoma, systemic lupus erythematosus (SLE), Wiskott-Aldrich syndrome, and severe combined immunodeficiency (SCID).<sup>8,10</sup> In a recent study, Calabrese et al.<sup>5</sup> reviewed 36 cases of PML associated with rheumatic disease. Each patient had been treated with various immunosuppressants before PML developed. Of all rheumatic conditions, such as rheumatoid arthritis, Wegener granulomatosis, dermatomyositis, polymyositis, and scleroderma, SLE was most commonly associated with PML (23/35 cases). The average age of those with SLE was 43 years and non-SLE was 50 years with females accounting for 19 of 23 cases. The presentation of PML was typical, with progressive neurologic deterioration occurring.

Radiographic evidence of PML strongly supports its diagnosis, with MRI being the imaging modality of choice. PML lesions may occur anywhere, most frequently seen at the grey-white matter interface, involving the subcortical U fibers of the parieto-occipital regions and frontal lobes. These lesions are initially multiple and discrete, but may

eventually coalesce into larger lesions. They most often are bilateral and asymmetric and rarely solitary.<sup>9,10</sup> Lesions confined to the posterior fossa are uncommon.<sup>11</sup>

CT scans usually demonstrate bilateral asymmetric hypodense foci without mass effect or enhancement. On MRI these lesions appear hyperintense in the T2WI, typically involving the subcortical and also the periventricular white matter. When in the subcortical white matter, fluid-attenuated inversion recovery (FLAIR) images are sensitive to demonstrate the demyelinating lesions, which appear hyperintense against a background of suppressed CSF signal intensity. Lesions appear hypointense and well demarcated on T1WI, although they may be isointense in the initial phase of the disease. Typically, PML lesions do not enhance, but faint peripheral enhancement has been described.<sup>12,13</sup>

It has been suggested that the appearance of DWI correlates with the stage of the disease and may be useful for documenting response of PML.<sup>9</sup> In active lesions a central core of facilitated diffusion often exists with a rim of diffusion restriction at the advancing edge which is typically incomplete.<sup>14</sup> Apparent diffusion coefficient (ADC) values have been reported to be much higher in the center of a lesion than at its periphery.<sup>15,16</sup> This radiologic appearance has been correlated with large oligodendrocytes, enlarged "bizarre astrocytes" with several large processes, and infiltration of foamy macrophages.<sup>6,17</sup> Diffusion restriction at the margin is due to either reduced extracellular space or enlarged cells, as the water is trapped in the intracellular space.<sup>18-20</sup> In older lesions, facilitated diffusion predominates. This is thought to be associated with disorganized cellular architecture, dead oligodendrocytes, which thereby increases extracellular space, macrophage action, and astrocytic repair responses.<sup>14</sup>

To date, there has been no specific treatment for PML. Several pharmacologic agents, such as cytarabine, cidofovir, and topotecan have been used in clinical trials to target JCV in the past. All studies did not show a clinical benefit which outweighed the risk of potential toxicity related to those drugs.<sup>6</sup> Discontinuation of immunosuppressant treatment has also traditionally been a treatment of choice.<sup>21</sup>

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