

## Progressive multifocal leukoencephalopathy: a challenging diagnosis established at autopsy

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**How to cite:** Lopes CCB, Crivillari M, Prado JCM, et al. Progressive multifocal leukoencephalopathy: a challenging diagnosis established at autopsy. *Autops Case Rep* [Internet]. 2019;9(1):e2018063. <https://doi.org/10.4322/acr.2018.063>

### ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a feared entity that occurs most frequently in conditions of extreme immunodeficiency. The diagnosis is often made long after the onset of symptoms due to the physicians' unfamiliarity, and the unavailability of diagnostic tests in some medical centers. Although the incidence of PML is decreasing among HIV patients with the advent of highly active antiretroviral therapy (HAART), in Brazil this entity is the fourth highest neurological complication among these patients. The authors present the case of a middle-aged man who tested positive for HIV concomitantly with the presentation of hyposensitivity in the face and the right side of the body, accompanied by mild weakness in the left upper limb. The clinical features worsened rapidly within a couple of weeks. The diagnostic work-up pointed to the working diagnosis of PML after brain magnetic resonance imaging; however, the detection of the John Cunningham virus (JCV) in the cerebral spinal fluid was negative. HAART was started but the patient died after 7 weeks of hospitalization. The autopsy revealed extensive multifocal patchy areas of demyelination in the white matter where the microscopy depicted demyelination, oligodendrocytes alterations, bizarre atypical astrocytes, and perivascular lymphocytic infiltration. The immunohistochemistry was positive for anti-SV40, and the polymerase chain reaction of the brain paraffin-embedded tissue was positive for JCV. The authors highlight the challenges for diagnosing PML, as well as the devastating outcome of PML among HIV patients.

### Keywords

Leukoencephalopathy, Progressive Multifocal, Acquired Immunodeficiency Syndrome, JC Virus, Diagnosis, Autopsy

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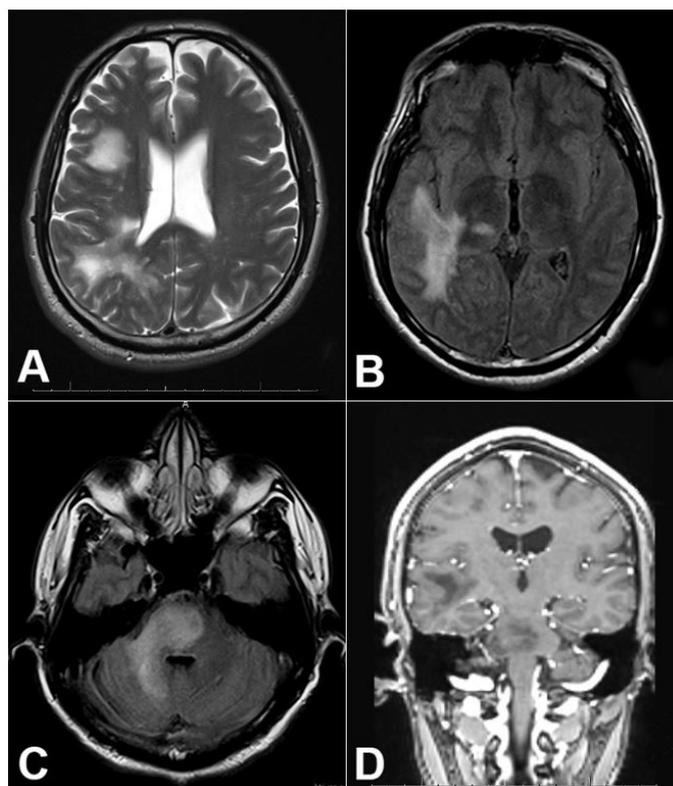


## CASE REPORT

A 43-year-old man presented to the emergency room complaining of tongue paresthesia, slurred speech, and weakness. These symptoms had developed insidiously and progressively over the past 4 weeks. The patient described muscular weakness initially involving the left side of the body, which soon included the right side. He also referred a decrease in sensitivity in the left half of the body. He denied fever, headache, weight loss, dyspnea, convulsions, visual symptoms, incontinence, and vertigo. His past medical history was unremarkable, except for smoking (15 pack-years) and recreational alcohol consumption.

The neurological examination revealed a hyposensitivity in the right hemiface, as in the right half of the body, and grade 4 of muscle strength of the left upper limb. The remaining physical examination was normal as were his vital signs. The initial laboratory work-up was normal; however, further investigation revealed a positive serology for HIV infection by the enzyme-linked immunosorbent assay and Western blotting. The TCD4+ peripheral count was 75 cells/ $\mu$ L, and the HIV-1 RNA viral load in the blood was 97,911 copies/mL (branched DNA) or Log 4.991. The brain computed tomography (CT) revealed two hypodense foci in the right cerebral hemisphere's white matter, in the right frontal lobe, and in the high parietal region, without contrast enhancement or midline shift.

Due to the imaging findings in a patient with HIV, neurotoxoplasmosis was the initial working diagnosis. Therefore, pyrimethamine and sulfadiazine were promptly prescribed. Two weeks later, this antibiotic regimen was withdrawn since (i) the patient's clinical features did not improve; (ii) the serology for toxoplasmosis tested negative for immunoglobulin IgG and IgM; and (iii) the lesions increased in size and became more evident in controlled CT. The brain magnetic resonance imaging (MRI) showed extensive discontinuous hyper signal areas on T2- and FLAIR-weighted images in the hemispheric white matter, with predominance in the right frontotemporal subcortical region, as well as in the splenium of the corpus callosum and the brainstem (Figure 1). These findings raised the diagnosis of PML. At this time, the cerebrospinal fluid (CSF) examination showed leukocytes of 2 cells, erythrocytes of 14 cells,



**Figure 1.** Brain MRI. **A** – T2 weighted axial image demonstrates subcortical e periventricular white matter lesions in the right hemisphere, without significant associated mass effect; **B** – Flair weighted axial image shows subcortical confluent lesions on the right temporal lobe, internal capsule and thalamus; **C** – Flair weighted axial image shows pontine and right middle cerebellar peduncle confluent lesions; **D** – Post contrast T1 weighted coronal image demonstrates lack of contrast enhancement in the aforementioned described lesions.

protein of 25 mg/dL, and glucose of 58 mg/dL. CSF culture was negative for bacteria, mycobacteria, and fungus. The polymerase chain reactions (PCR) for *Mycobacterium tuberculosis*, *Cryptococcus* spp, *Toxoplasma gondii*, and JCV were negative, which permitted the initiation of highly active antiretroviral therapy (HAART).

The patient's outcome was troublesome with progressive worsening of his neurological status, and slow progression to spastic paraparesis. At the end of the fourth week of hospitalization the patient maintained only the distal movement of the right upper limb, hyperreflexia, tetraplegia in a pyramidal pattern, generalized spasticity and hypertonia, ophthalmoplegia, facial amimia, gaze fixation inability,

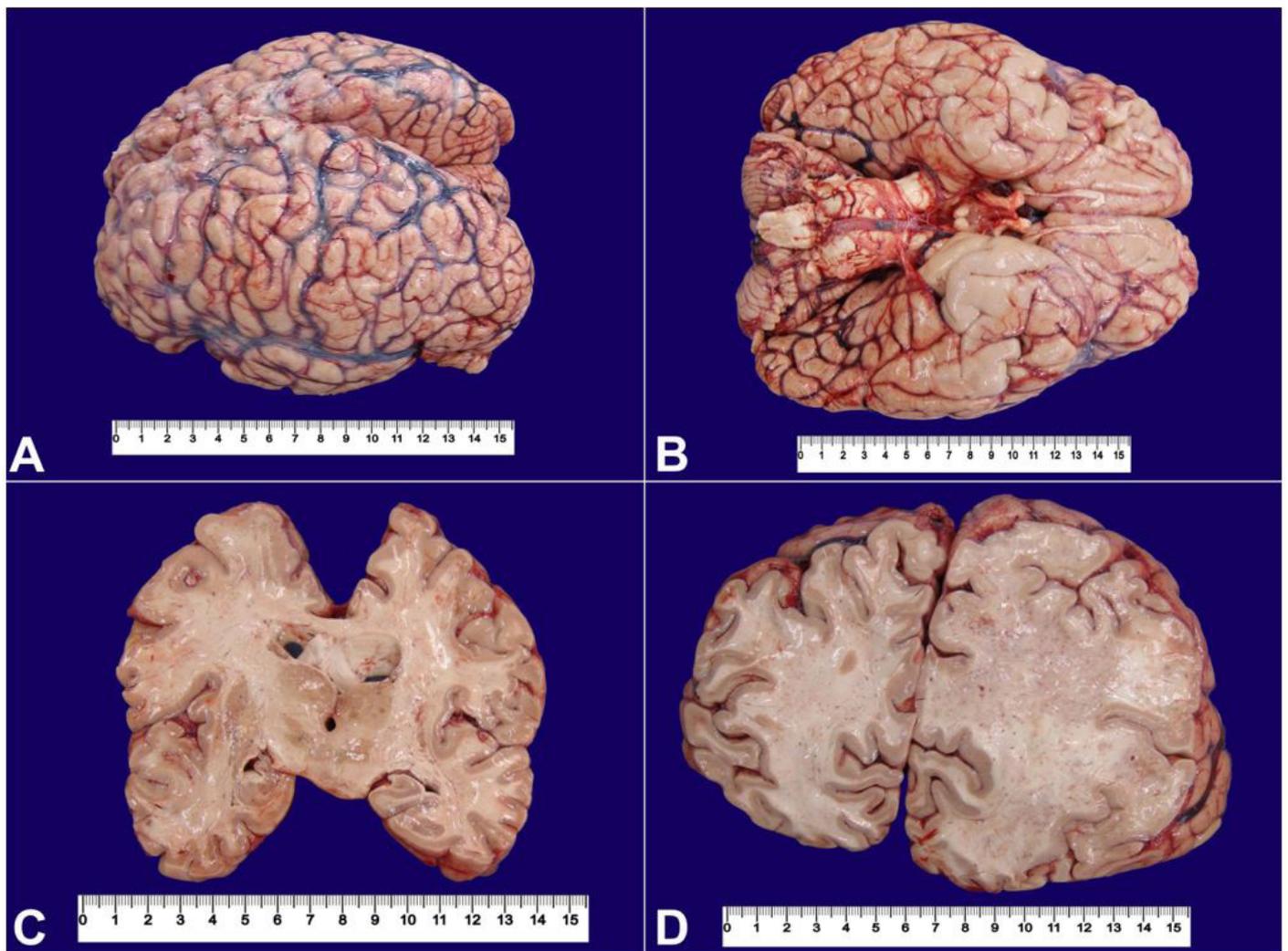
anarthria, and the inability to swallow. According to this outcome, the diagnosis of PML was highly considered, and because of the deterioration of the neurological status concomitantly after HAART, the hypothesis of immune reconstitution inflammatory syndrome-PML (IRIS-PML) was considered. Thus, prednisone 1 mg/kg was started. However, no improvement was observed.

Meanwhile, the patient presented an episode of bronchoaspiration and septic shock, and died after 7 weeks of hospitalization.

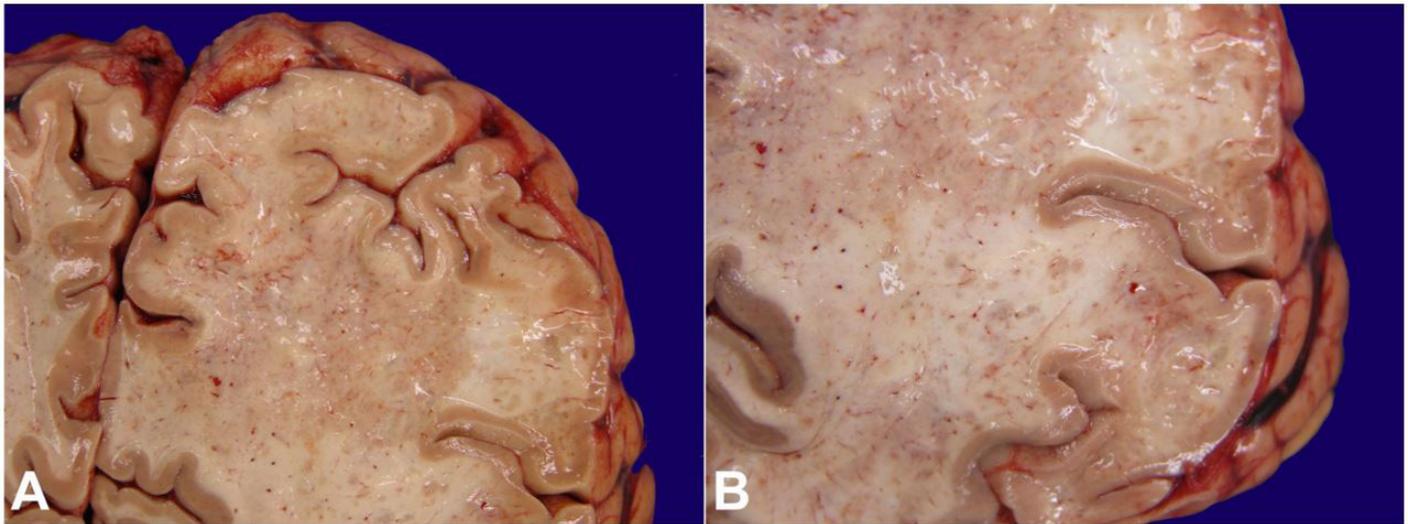
An autopsy was performed after the informed consent signed by his wife.

## AUTOPSY FINDINGS

The examination of the central nervous system (CNS) showed vascular congestion in the meninges with mild cerebral edema (Figure 2A). The vessels of the circle of Willis were preserved (Figure 2B). The coronal section depicted small, irregular, and ill-defined brownish patches involving the white matter and the basal ganglia. These lesions were more prominent in the right hemisphere, where the patches in the subcortical topography became confluent (Figures 2C, 2D, and Figure 3).



**Figure 2.** Gross findings of the brain. **A** – Vascular congestion in the meninges and generalized edema characterized by flattened gyri and narrowed intervening sulci; **B** – Inferior and posterior view showing edema, but without signals of herniation. The circle of Willis vessels were preserved; **C** – Coronal section of the brain showing small, irregular, and ill-defined brownish patches of white matter, also compromising the basal ganglia; **D** – Presence of poorly defined areas of brownish patches in the subcortical topography, which became confluent plaques in the white matter, especially in the right parieto-occipital hemisphere.



**Figure 3.** Gross examination of the cutting surface of the brain. **A** and **B** – Coronal section showing in detail the ill-defined brownish patches to confluent plaques in the white matter, with poorly defined limits between gray and white matter.

On microscopy, the boundary between the gray and the white matter was blurred by chronic inflammatory infiltrate with an increase in the number of oligodendrocytes, which showed typical glassy chromatin nuclei of viral inclusion. In the white matter, the parenchyma was disrupted by a dense infiltration of foamy macrophages, reactive astrocytes (which sometimes had bizarre atypical appearance), and perivascular lymphocytic inflammation (Figure 4).

The immunohistochemistry study was positive for simian virus 40 (SV40) (clone MRQ-4, Cell Marque), which cross-reacts with polyomavirus (Figure 5), and was negative for cytomegalovirus and herpesvirus. The presence of the JC polyomavirus (JCPyV) was also detected in the formaldehyde-fixed, paraffin-embedded, CNS by the specific amplification of genetic material from the DNA sample. For this purpose, the primers described by Agostini et al.<sup>1</sup> were used along with DNA isolates from samples previously known as positives and negatives. Thus, the presence of genetic material of JCPyV in the neural tissue of the patient was assured.

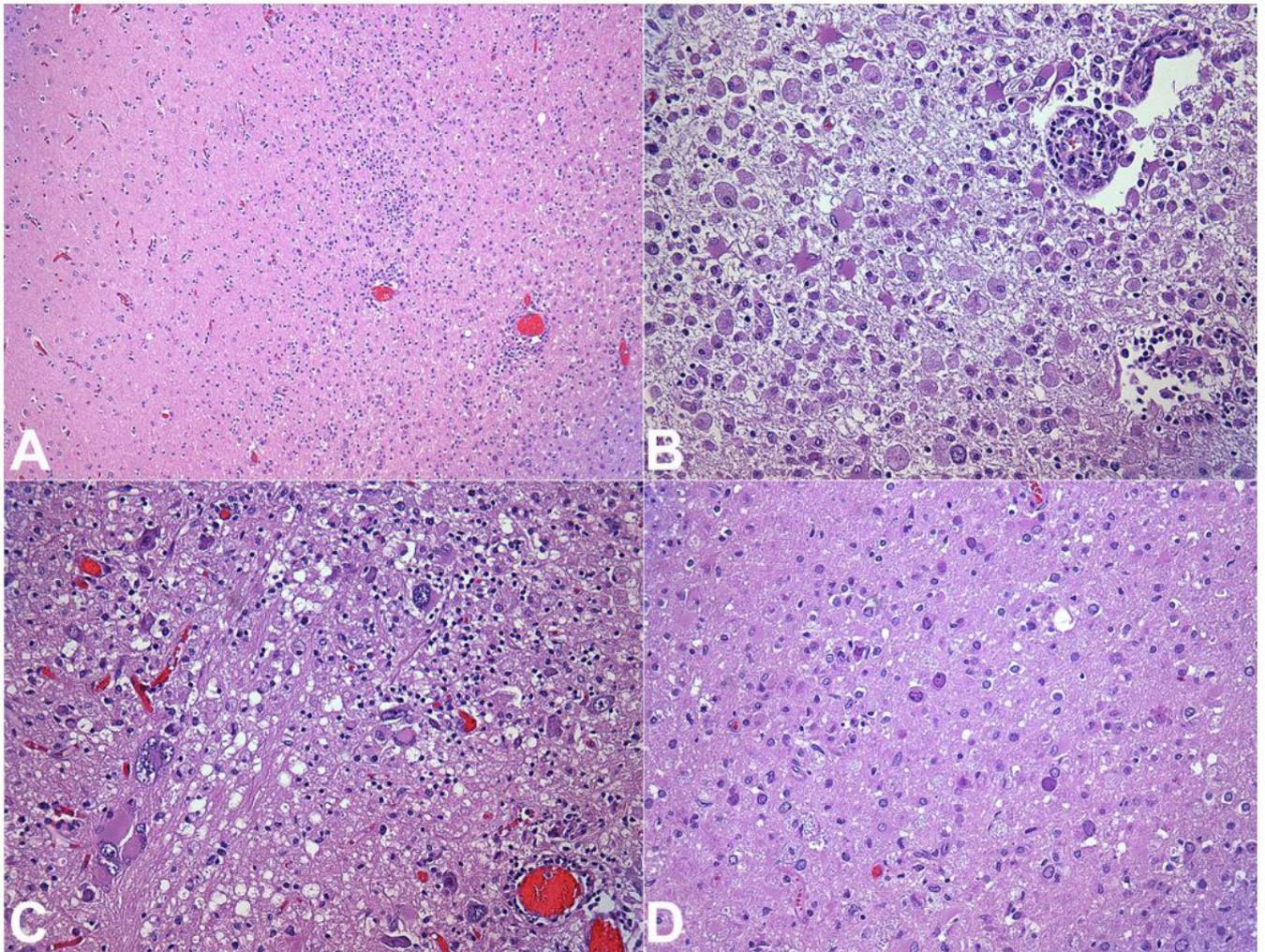
The lungs were congested and heavy. The microscopic examination revealed a diffuse alveolar edema and bronchopneumonia, possibly secondary to bronchoaspiration (Figure 6A). The pancreas examination showed necrosis and steatonecrosis (Figure 6B), while the kidney's histology presented acute tubular necrosis—the findings of which were

consistent with a final outcome due to hemodynamic shock. There was also zone 3 passive congestion in liver parenchyma. Another finding related to AIDS was the splenic white pulp lymphocytic depletion (Figure 6C) and a focal chronic inflammatory infiltration in adrenal parenchyma (Figure 6D).

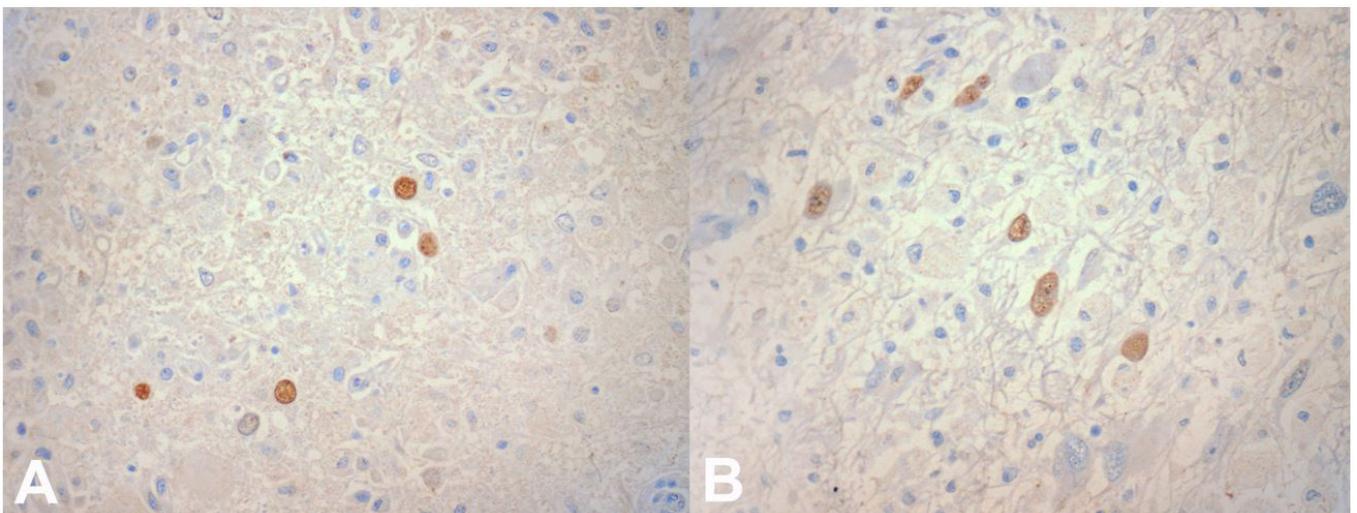
## DISCUSSION

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the CNS characterized by injury to the glial cells—in particular, the oligodendrocytes—caused by a polyomavirus called JCV. PML mostly occurs in immunosuppressed patients, and presents with a progressive, disabling, and often fatal clinical course. Since the HIV epidemic and the emergence of new immunosuppressive drugs, PML has become a significant source of concern and research.<sup>2,3</sup>

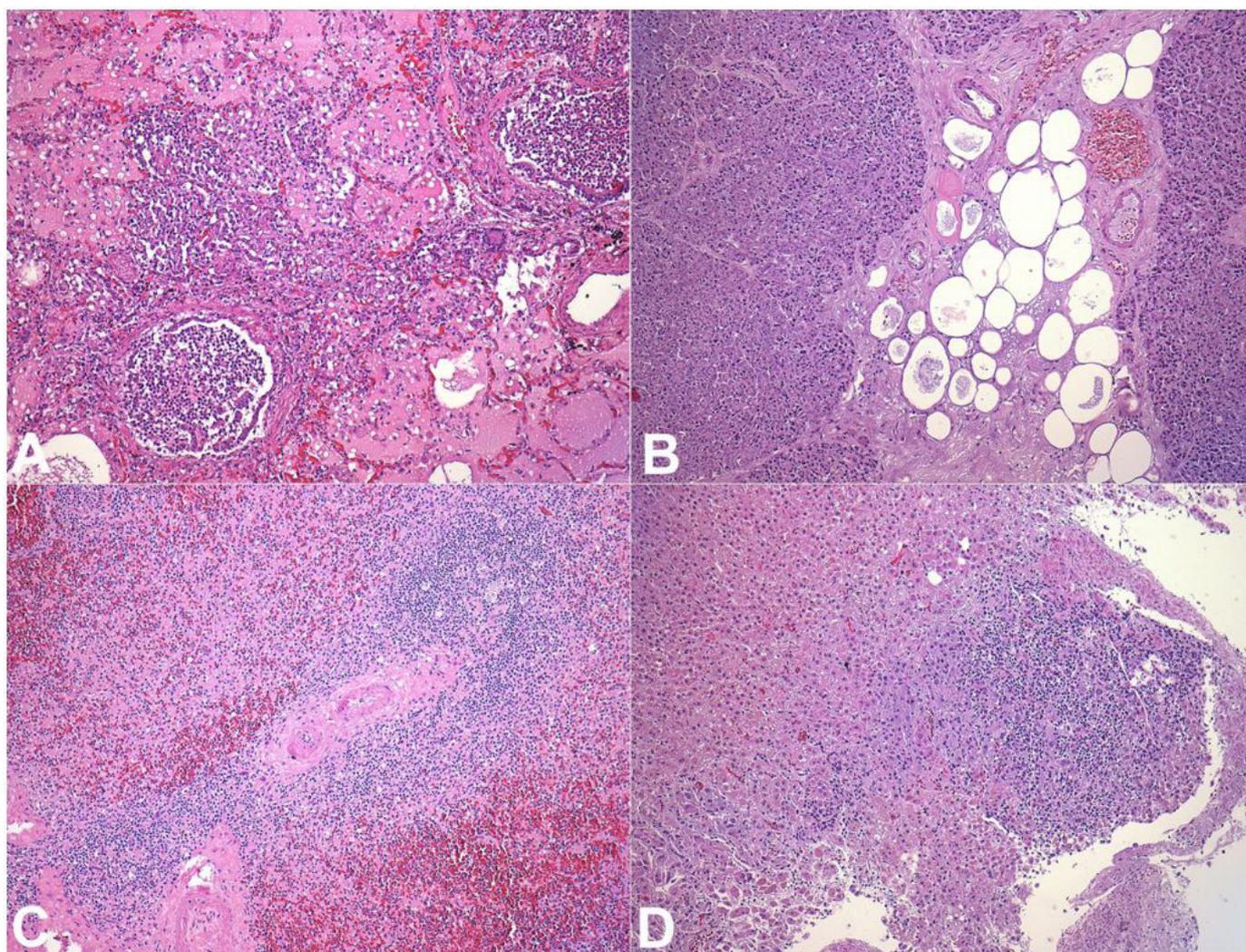
In the 1950s, the cytotechnologist, Andrew Ricci, initially observed cells with large homogeneous nuclei in the urine, which he christened the “decoy cells” because of their benign origin mimicking cancer cells. The nature of the “decoy cells” was clarified in 1971 when Gardner et al.<sup>4</sup> isolated the human polyomavirus from the urine of a renal transplant recipient with initials BK.<sup>5</sup> This virus is a non-enveloped DNA viral group that belongs to the Polyomaviridae family, which infects humans, as well as apes, rodents, and parakeets. In humans, the infection is caused by the



**Figure 4.** Photomicrographs of the brain. **A** – The limit between gray and white matter was blurred by chronic inflammatory infiltrate with augmented oligodendrocytes (H&E 100X); **B** – White matter parenchyma with dense infiltration of foamy macrophages, reactive astrocytes, and perivascular lymphocytic inflammation (H&E 200X); **C** – Detail of the reactive astrocytes showing bizarre atypical nuclei (H&E 400X); **D** – Gray matter with augmented oligodendrocytes showing typical glassy chromatin nuclei of viral inclusion (H&E 400X).



**Figure 5.** Photomicrographs of the brain. **A** and **B** – Immunophenotype positive for simian virus 40 highlighting the cells infected by the JCV. (Immunohistochemistry 400X).



**Figure 6.** Photomicrographs. **A** – Lung: pulmonary parenchyma showing bronchopneumonia and diffuse alveolar edema (H&E 100X); **B** – Pancreas: parenchyma showing diffuse ischemic necrosis with focal steatonecrosis (H&E 100X); **C** – Spleen: presence of white pulp lymphocytic depletion (H&E 100X); **D** – Adrenal: presence of focal chronic inflammatory infiltration in adrenal parenchyma (H&E 100X).

BK virus, which is associated with nephropathy in transplanted recipients, and JCV, which causes PML.<sup>6</sup>

The JCV is distributed worldwide with a prevalence of 50-70%.<sup>7-9</sup> The transmission occurs through the fecal-oral and respiratory routes, and by tissue donation. The polyomavirus causes a latent asymptomatic infection with a persistent cycle of replication, which contributes to the spread of the virus. The replication cycles are associated with fluctuations of the immunity status, such as pregnancy and senility, or with severe immunosuppression, which occurs after transplant, chemotherapy, or HIV infection.

Rare cases of PML in immunocompetent patients with or without an underlying disease have been reported.<sup>10</sup> Those with an underlying disease have been

defined as PML in the presence of occult or transient immunosuppression, namely (i) hepatic cirrhosis; (ii) chronic renal failure; (iii) pregnancy; (iv) dementia; and (v) dermatomyositis.<sup>11</sup> Thus, PML should be considered in the differential diagnosis of patients with new-onset neurological symptoms, even without overt immunosuppressive risk factors.

Over the years, the origin of the underlying immunosuppression has been changing because of the improvement in HIV treatment, and the emergence of new and widely used immunosuppressive drugs. A recent study on the incidence of PML in Sweden over 3 decades showed that HIV infection was the leading cause of immunosuppression in the first fifth (1988-1992) of the study period, representing 48% of

cases of PML. However, in the last fifth of the study period (2008-2013), the autoimmune diseases took the lead (39% of the cases), while HIV infection dropped to 11%.<sup>12</sup> Similarly, other studies showed a decline in the incidence of PML among HIV patients in Denmark<sup>13</sup> and Switzerland.<sup>14</sup>

Despite this declining incidence, PML remains a significant CNS complication of patients with HIV/AIDS. A Brazilian study showed that PML was the fourth most frequent opportunistic infection in AIDS patients after toxoplasmosis, cryptococcal meningoencephalitis, and neurotuberculosis.<sup>15</sup>

Clinically, PML can present a broad constellation of neurologic signs and symptoms due to its ability to affect virtually any area of the brain, and the frequently multifocal nature of the lesions.<sup>2,3</sup> Thus, it is difficult to establish a topographic neurological diagnosis, similar to that which occurs with other demyelinating diseases. The most common clinical features comprise motor weakness (hemiparesis or monoparesis), cognitive dysfunction, appendicular or gait ataxia, visual symptoms (hemianopsia, diplopia), and speech disturbances. Sensory loss, seizures, headache, and aphasia occur less frequently.<sup>12,13,15,16</sup> In our case, the patient presented with motor weakness, impaired gait, speech disturbance, and sensory loss, which were consistent with the most cited features of PML.

Based on the CT images and the positive result for HIV tests, neurotoxoplasmosis was the initial working diagnosis because of its leading cause of CNS infection in AIDS patients. The current treatment for neurotoxoplasmosis is highly effective and is accompanied by a rapid clinical recovery. In a large clinical series of patients,<sup>17</sup> 74% showed improved in their symptoms by day 7 of therapy, and 91% of them by day 14. Thus, it is reasonable to conclude that the failure of toxoplasmosis treatment should raise the suspicion for other differential diagnoses. In our case, the therapeutic failure after 2 weeks, which was associated with the negative serology for toxoplasmosis, made the diagnosis of neurotoxoplasmosis unlikely, and the suspicion for PML increased.

With the increase in knowledge regarding PML, and the new techniques that help to diagnose JCV, new forms of CNS involvement and, therefore, new forms of clinical syndromes (hitherto not well-known) have been described; such as (i) JCV granule cell neuropathy leading to a cerebellar syndrome; (ii) JCV

encephalopathy due to cortical grey matter impairment; and (iii) JCV meningitis, which leads to meningeal syndrome without evidence of brain lesions.<sup>2,3</sup>

The diagnosis of PML faces some obstacles, such as its low incidence, the unfamiliarity of it among most physicians, and the eventual unspecificity of the clinical features and neuroimaging. The latter may mimic stroke, brain tumor, or cerebral toxoplasmosis, which often retard the diagnosis. In a retrospective study involving 111 PML cases,<sup>18</sup> the median time from the initial symptoms to diagnosis was 74 days. In this study, misdiagnoses were done in nearly two-thirds of cases, and more than three-quarters of patients had their diagnosis delayed for more than 1 month. To avoid this delay, the inclusion of PML in the differential diagnosis of CNS lesions in patients with known risk factors together with early work-up directed towards this entity seems to be the better procedure.

In 2013, the Neuroinfectious Disease Section of the American Academy of Neurology proposed the criteria<sup>9</sup> to establish the diagnosis of PML. PML diagnosis is considered to be definitive by (i) securing the diagnosis with tissue sample; or (ii) determining the diagnosis with compatible clinical and radiographic features coupled with the demonstration of the virus in CSF. A lack of one or more of the aforementioned findings alters the diagnostic characterization to probable or possible. Therefore, in our case, the *in vivo* diagnosis of PML was considered possible due to the lack of demonstration of JCV in the CSF.

The diagnosis based on neuropathology usually is not that difficult if the specimen shows the demyelination, the hyperchromatic and enlarged oligodendroglial nuclei, and the enlarged bizarre astrocytes with lobulated hyperchromatic nuclei accompanied by the detection of JCV.<sup>9</sup> However, the arduous task relies on obtaining the brain tissue. Although brain biopsy has been proved to be an effective way of diagnosing intracranial lesions, it requires a highly-specialized team and costly resources. The procedure is associated with a significant risk of fatal complications and a high index of morbidity. Moreover, the lesions may not be readily accessible, the biopsy size may be insufficient, and sometimes the patient's clinical status does not allow the procedure to be undertaken.<sup>19-21</sup>

The detection of JCV in the brain tissue of PML may be achieved by immunohistochemistry (IHC)

using commercially anti-SV40 monoclonal antibody, in situ hybridization (ISH) and PCR. Zivanovic et al.<sup>21</sup> reported the comparison of these three methods in a series of seven cases (four biopsies and four autopsies; one case had biopsy and was autopsied as well) and concluded that ISH was the more sensitive method followed by PCR and IHC, and recommended using a combination of at least two different methods for JCV detection. Muñoz-Mármol et al.,<sup>22</sup> studying 14 paraffin-embedded postmortem brain specimens, showed better sensitivity for IHC and PCR. In this series, the IHC was more sensitive for the PAb 2003 antibody compared to the antibody anti-SV40.

In our case, in vivo brain biopsy was unavailable and the definitive diagnosis of PML was made by postmortem tissue analysis. Along with the typical gross findings in autopsy, the microscopy was rich and consistent with the typical descriptions of the JCV histological findings. The IHC with anti-SV40 and the PCR were positive in the CNS tissue sample. It is worth pointing out that the number of altered oligodendroglial cells were high, which increased the chances of detecting the virus by using the different methods.

Because of the cited obstacles for performing brain biopsy, the diagnosis of PML commonly relies on the analysis of the CSF. However, the PCR for JCV is not widely available in some medical centers, and its sensitivity decreases with HAART. Marzocchetti et al.<sup>23</sup> compared the sensitivity of JCV by PCR in the CSF of HIV patients with suspected PML between 1992 and 2002, and found a drop in the positive detection from 89.5% in the pre-HAART era (1992-1995) to 57.5% in the HAART era (1996-2002), but no changes in the specificity were observed. Similarly, this discrepancy concerning the sensitivity of PCR tested in the CSF was observed comparing the studies of McGuire et al.<sup>24</sup> and Bossolasco et al.<sup>25</sup> The former found a sensitivity of 92% in the pre-HAART era (1995) and the latter found 76% in the HAART era (2005).

The radiologic investigation helps to make the diagnosis and may allow its distinction from other diagnoses.<sup>9</sup> MRI is the most appropriate examination for PML work-up since it detects early lesions. PML lesions appear as hyperintense areas in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, and as hypointense areas in T1-weighted images. In CT scans, brain lesions appear as asymmetric multifocal

areas of hypodensity. These lesions are frequently asymmetric, bilateral, and multiple, although they may occasionally be solitary, with variable shape and size, which become confluent and extensive with the progression of the disease. They are mainly subcortical and are located almost exclusively in the white matter, although eventual extension to the gray matter has been reported. Usually, there is no mass effect even in the extensive lesions, nor contrast enhancement.<sup>9,26-28</sup>

As reported in our case, the hypodense brain lesions found in the CT were non-specific, and did not add any information to achieve the final diagnosis. Neurotoxoplasmosis was assumed as the working diagnosis even in the absence of the typical contour contrast enhancement. Indeed, this finding may be absent or faint when CD4 is below 50 cells/mm<sup>3</sup>.<sup>29</sup> In fact, the diagnosis of PML was highly considered after the MRI despite the negative PCR for JCV result in CSF.

Several therapeutic regimens including cytarabine, camptothecin, topotecan, and cidofovir were studied and proposed as the PML treatment. These drugs have an anti-JCV replication action in vitro; however, the in vivo results were disappointing.<sup>3</sup> The serotonin receptor blocker was also tested after the discovery of the interaction between JCV and serotonin receptors 5-HT-2a from glial cells.<sup>2</sup> Nonetheless, no statistical significance in 1-year survival was observed between patients treated with mirtazapine and a control group.<sup>30</sup> Thus, no specific, effective treatment for JCV is currently available. The most effective therapy for PML relies upon the early onset of HAART.<sup>31</sup>

One of the management challenges of PML and other infections associated with AIDS remains the identification of the immune reconstitution inflammatory syndrome (IRIS), which is characterized by clinical deterioration, despite virological clearance, usually within 4-8 weeks after the HAART outset. The pathophysiology of IRIS is not yet fully understood, but seems to be attributed to an exacerbated inflammatory response modulated by the presence of the opportunistic agent or its antigens. In the context of PML, IRIS can occur both in its "unmasking" form—when the previously asymptomatic patient begins to present symptoms after HAART prescription—or in its "paradoxical" form, which arises during or after PML's treatment, when new clinical symptoms or worsening of the pre-existing symptoms arise. The latter often raises doubts as to whether there is a progression of

PML or if it corresponds to an overlap with IRIS, along with the possibility of HAART's adverse effects.<sup>32</sup>

The diagnosis of IRIS should be suspected whenever the clinical features of PML worsen or start 4-8 weeks after the introduction of HAART, and the CD4+ is <100 cell/mm<sup>3</sup> before the onset of HAART; or when an immune or virological response is observed after the HAART onset. In the case presented herein, IRIS was suspected because the neurological worsening coincided with the third week of HAART.

The diagnosis or suspicion of IRIS should not motivate the withdrawal of HAART. Untreated HIV patients with the diagnosis of PML show an increment in survival rate with HAART from 10% to 43-75%.<sup>33-35</sup> The management of IRIS consists of using a non-steroidal anti-inflammatory drug in mild cases, or prednisone at a dose of 1-2mg/kg, or equivalent, for 1-2 weeks in more severe cases. However, the use of anti-inflammatory agents to treat PML-IRIS remains debatable. A French review<sup>32</sup> showed that corticosteroid therapy did not change the outcome of patients with PML-IRIS, and suggested that the corticosteroid prescription should be reserved for patients with severe neurological symptoms and/or massive cerebral inflammation, or brain herniation. In our case, prednisone was prescribed due to severe neurological worsening, but no improvement was observed.

The clinical course of PML remains dreadful. However, the survival rate has improved over the years, which is probably related to the growing efficacy of HAART. In the pre-HAART era, Berger et al.<sup>33</sup> reported a median survival of 6 months for AIDS-related PML, and only in 9% did the survival exceeded 1 year. In the Danish cohort study,<sup>13</sup> the median survival time increased from 0.4 years in those diagnosed with PML before 1997 (pre-HAART era) to 1.8 years in those diagnosed with PML from 1997 to 2006. Despite the increment in the survival rate after HAART, most PML survivors present sequelae. In our case, the disease followed the progressive course without any remission period, leading to a fatal outcome approximately 3 months after the initial symptoms.

## CONCLUSION

Although PML is rare, clinicians should always keep this possibility in mind while working up diseases with a similar clinical presentation. Every immunosuppressed

patient with CNS injury should include PML in the diagnostic process. A CT scan is non-specific and unreliable, and it may delay or mask the diagnosis. Therefore, MRI should—whenever possible—be requested, since it may be the primary diagnostic clue. Tissue samples accompanied by immunopathological and molecular studies should always be pursued to reach a definitive diagnosis. Nevertheless, much remains to be discovered and researched concerning PML and other polyomavirus-related diseases, as well as their best treatment.

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**Author contributions:** Lopes CCB, Crivillari M, Prado JCM, Ferreira CR, Santos Neto PJ, Takayasu V, Laborda LS collectively and equally contributed to the manuscript preparation. Similarly, all authors proofread and approved the manuscript's final version for publication.

**Conflict of interest:** None

**Financial support:** None

**Submitted on:** September 29<sup>th</sup>, 2018

**Accepted on:** November 13<sup>th</sup>, 2018

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