

# Progressive multifocal leukoencephalopathy, a rare entity with a fatal outcome. Case presentation

## Leucoencefalopatía multifocal progresiva, una entidad rara con un desenlace fatal. Presentación de caso

**Key words (MeSH)**

Leukoencephalopathy progressive multifocal
JC virus
Acquired immunodeficiency syndrome
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**Palabras clave (DeCS)**

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## Summary

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection caused by the reactivation of the John Cunningham neurotrophic virus, which develops an infectious process in cases of severe immunosuppression. Magnetic resonance imaging is the preferred imaging method for diagnosis. Imaging characteristics include the identification of asymmetric and generalized areas in the white matter, with high signal intensity in T2-weighted sequences, little mass effect, diffusion restriction and little enhancement after administration of contrast medium. We present the case of a 31-year-old patient with a clinical course of neurocognitive deterioration, with magnetic resonance findings compatible with PML. The main characteristics and key points for imaging diagnosis will be described.

## Resumen

La leucoencefalopatía multifocal progresiva (LMP) es una infección oportunista causada por la reactivación del virus neurotrófico John Cunningham, el cual desarrolla un proceso infeccioso en casos de inmunosupresión grave. La resonancia magnética es el método de imagen preferido para el diagnóstico. Las características por imagen incluyen la identificación de áreas asimétricas y generalizadas en la sustancia blanca, con alta intensidad en señal en secuencias potenciadas en T2, escaso efecto de masa, restricción a la difusión y escaso realce tras la administración del medio de contraste. Se presenta el caso de un paciente de 31 años de edad, con un curso clínico de deterioro neurocognitivo, con hallazgos en la resonancia magnética compatibles con LPM. Se describirán las principales características y puntos clave para el diagnóstico imagenológico.

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## Introduction

Progressive multifocal leukoencephalopathy (PML), first described in 1958 by Åström et al., is an opportunistic infection caused by reactivation of the neurotrophic John Cunningham virus (JCV) of the Polyomaviridae family. Eleven other human viruses of this family have been identified. The number and variety of JCVs in humans reflect their ability to spread at low levels without causing disease and evading the immune system. Most polyomaviruses establish asymptomatic infection in healthy hosts and are pathogenic only in cases of severe immunosuppression (1). The requirement described is profound suppression of cell-mediated immunity, as in acquired immunodeficiency syndrome (AIDS), lymphoproliferative malignancies, immunosuppressive or immunomodulatory therapies in multiple sclerosis (MS) or rheumatoid arthritis (RA) or both (systemic lupus erythematosus). Transmission occurs through person-to-person contact, as well as through contact with contaminated surfaces, food, and water. The virus enters through the oropharynx and spreads hematogenously, affecting the bone marrow, lymphoid tissue, and brain (2). In the brain, the infection affects

the white matter (mainly oligodendrocytes) and brain neurons, causing irreversible demyelination and axonal damage (3).

The diagnostic criteria for PML are based on clinical presentation, brain magnetic resonance imaging (MRI) findings, and demonstration of JC virus DNA, either by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) or by histopathology (4).

MRI is the preferred imaging method for diagnosing PML. Imaging features include asymmetric, generalized white matter lesions with high signal intensity on T2-weighted sequences and little mass effect. The FLAIR (Fluid Attenuated Inversion Recovery) sequence shows high-signal punctate lesions surrounding the main area of the lesion, also described as a "milky appearance" or "Milky Way sign." In addition, these lesions have a perivascular distribution pattern suggestive of inflammation. PML lesions have been described as having poorly defined borders toward the white matter and sharp borders toward the gray matter (5).

The "barbell sign" can be seen on the PML, which is defined as a bilateral occipitoparietal coalescent lesion, with a high signal on FLAIR images, extending across the splenium of the corpus callosum and involving the subcortical fibers with minimal or no mass effect, without enhancement after contrast administration and with a thin edge of peripheral diffusion restriction (6).

Another sign that has been described in PML is the "shrimp sign," which is a well-defined lesion with high signal intensity on T2- or FLAIR-weighted sequences and low signal intensity on T1-weighted sequences in the cerebellar white matter that contacts but spares the dentate nucleus and gives the appearance of a "shrimp"; In turn, it can affect the hilum of the dentate nucleus. On axial MRI images, the well-defined white matter lesion delineates the dentate nucleus in a curvilinear and sinuous manner (7).

Additionally, the "Easter bun sign" has been described, which represents a cross-shaped abnormality in the center of the pons in T2-weighted images, due to the selective loss of myelinated pontocerebellar fibers and neurons in the pontine raphe, preserving the pontine tegmentum and corticospinal tracts, and is observed in the late course of PML; this sign is characteristic and more common in multiple system atrophy. Involvement of the posterior fossa structures may also be observed, as the brainstem and cerebellum lose considerable volume in relation to olivopontocerebellar atrophy (6).

Generally, lesions in PML do not enhance after contrast administration; however, this has been observed in approximately 30% of patients. Enhancing lesions are usually seen in immune reconstitution inflammatory syndrome (IRIS), AIDS, and patients receiving monoclonal antibodies such as natalizumab, which is widely used in multiple sclerosis. When enhancement occurs after contrast administration, with the exception of the above-mentioned conditions, it may be associated with increased survival (8, 9).

In PML, diffusion restriction has a distinctive pattern that varies depending on the stage of the disease. Newer lesions and the edges of large lesions show a high signal on diffusion-weighted imaging (DWI) and a low or normal apparent diffusion coefficient (ADC), indicating active infection and cellular inflammation. In contrast, older lesions and the centers of large lesions show a low signal on DWI and a high ADC, suggesting areas of reparative gliosis (10).

The overall DWI lesion burden correlates with disease duration and severity, as measured by clinical scales such as Karnofsky and EDSS. Lesions with a central core of low signal on DWI and high ADC are associated with worse clinical stage and longer disease duration (11).

DWI images can identify areas of active disease progression before they are evident in other MRI sequences. In addition, the extent of diffusion abnormalities correlates with the rate of clinical progression, making DWI a valuable tool for assessing disease activity and response to treatment (12, 13).

Likewise, a homogeneous spectroscopic pattern can be observed, characterized by a decrease in the NAA/Cr (N-acetyl aspartate/creatine) ratio and an increase in the lactate/Cr (creatine), Co/Cr (choline/creatine), and lipid/Cr ratios. This pattern could be interpreted as a decrease in NAA, presence of lactate, and an increase in Co and lipids. However, as creatine concentration may decrease in PML, the other metabolites would appear to be higher than their actual concentration (14).

## Case report

A 31-year-old man with a recent diagnosis of human immunodeficiency virus (HIV) infection (CD4: 100 cells/mm3 and viral load of 163,623 copies/mL), without antiretroviral therapy; who presented with three months of episodes of special disorientation accompanied by anxiety, psychomotor agitation, gait disturbances (ataxia with rightward gait deviation), holocranial headache, and involuntary weight loss of approximately 8 kg in one month. The patient was evaluated by Psychiatry and prescribed sertraline 50 mg, with no improvement. On physical examination, he was uncooperative, disoriented in all three spheres, with horizontal nystagmus and multiple adenomegaly. Among the diagnostic images performed, the computed tomography (CT) scan of the skull showed irregular intra-axial areas of low density, compromising the white matter of the splenium of the corpus callosum with extension to the bilateral temporoparietal region (Figure 1). Additionally, a brain MRI was performed, which showed diffuse areas of low signal intensity with irregular and poorly defined edges on T1-weighted sequences, high signal intensity on T2-weighted and FLAIR sequences, with areas of medium intensity in the CSF (Figure 2); areas of diffusion restriction located in the splenium of the corpus callosum extending to bilateral periventricular white matter, midbrain, pons, bilateral middle cerebellar peduncle, and cerebellar hemispheres (Figure 3). After contrast administration, some areas of diffuse punctiform enhancement were observed within the areas described (Figure 4). Multivoxel spectroscopy with long echo time (135 msec) showed loss of the Co/Cr ratio due to a significant increase in the Co peak, decrease in the NAA peak, and lipid peak, related to cell membrane proliferation, neuronal damage, and necrosis. The CSF sample revealed few mature lymphocytes with PCR isolation of JC virus. During his hospital stay (32 days), the patient had progressive torpid evolution, persistent rigidity, tremor, left hemiparesis, impaired consciousness, and lethargy; he eventually died.

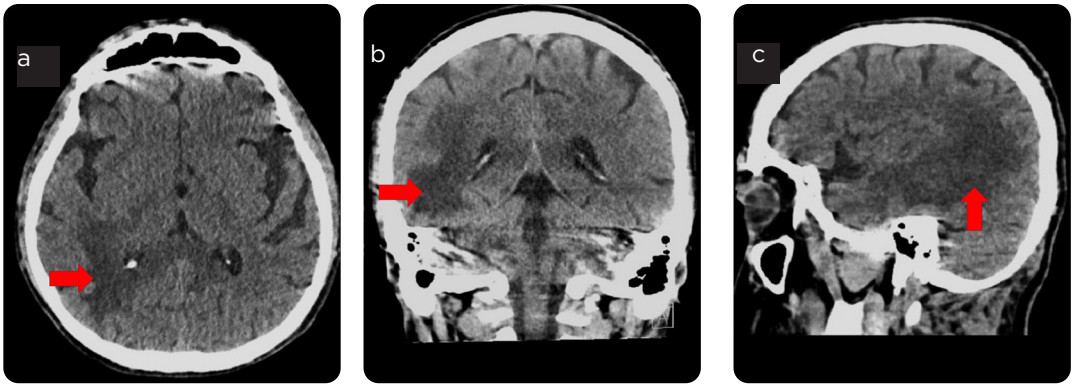



Figure 1. Non-contrast CT scan of the skull. a) Axial slice. b) Coronal reconstruction. c) Sagittal. Low-density, irregular intra-axial supratentorial image involving the right temporoparietal white matter (arrows).

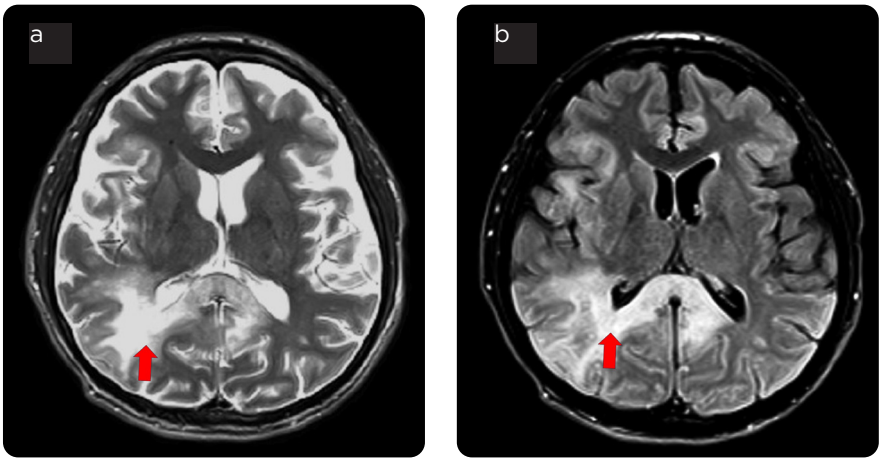



Figure 2. Axial brain MRI. a) T2-weighted and b) FLAIR of basal ganglia. Diffuse, irregular areas of high signal involving the splenium of the corpus callosum and the right temporoparietal white matter (arrows).

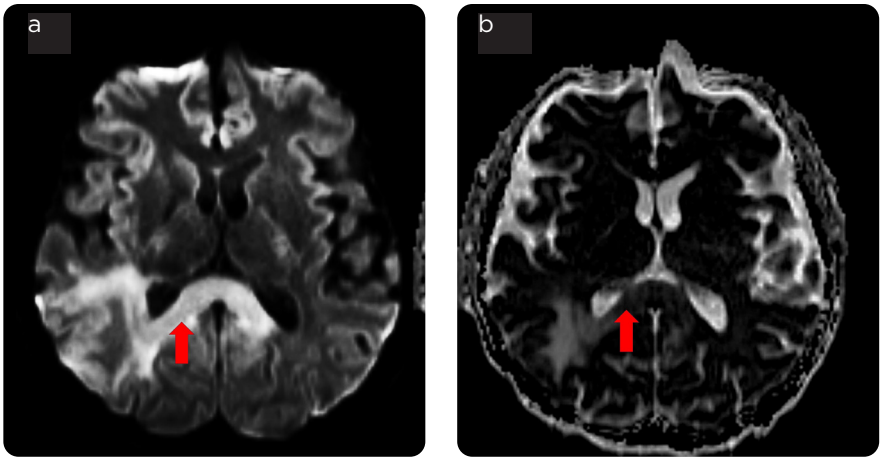



Figure 3. Axial brain MRI. a) Diffusion-weighted and b) ADC of the basal ganglia, with areas of diffusion restriction in the splenium of the corpus callosum and the right temporoparietal white matter (arrows).

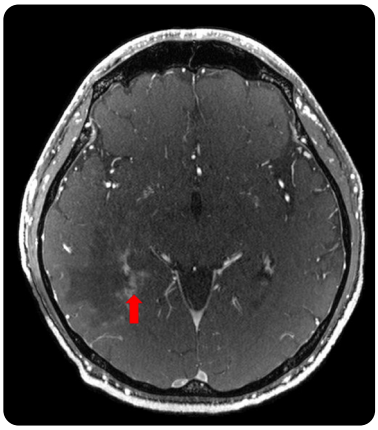


Figure 4. Axial T1-weighted contrast-enhanced brain MRI of the basal ganglia. Punctiform areas with enhancement after contrast administration in the right temporoparietal subcortex (arrow).

## Discussion

The diagnosis and treatment of PML became a major concern given the high rate of immunosuppression diagnosed each year (patients with multiple sclerosis treated with natalizumab and the growing number of cases of HIV infection) (15). PML, initially described in 1 in 200,000 inhabitants, is on the rise. In 80% of reported cases, it is associated with HIV infection, while the remaining 20% correspond to hematological malignancies, transplant recipients, and chronic inflammatory diseases (15).

The diagnosis of PML is generally based on neuroimaging, in the appropriate clinical context, and is confirmed by CSF PCR to document JCV DNA. Because PML lesions can involve multiple areas of the brain, clinical and imaging manifestations can vary (16).

In patients receiving immunotherapy in routine practice, differentiating PML from new multiple sclerosis lesions on brain MRI becomes a challenge for both neurologists and neuroradiologists. In summary, characteristic features of PML include a multifocal distribution of irregular or confluent areas of white matter signal abnormalities in the cerebral hemispheres, brainstem, and cerebellum. The absence of contrast enhancement and the absence or minimal mass effect have been used to distinguish PML from other entities that frequently occur in immunocompromised hosts, such as lymphoma and toxoplasmosis. The presence of punctate lesions on T2-weighted sequences appears to be one of the most important imaging features to consider in daily practice; DWI-weighted images in MRI of PML provide crucial information for the diagnosis and follow-up of the disease. When they have a high signal on DWI and low ADC, they represent active stages of the disease; conversely, if their signal on DWI is low and high on ADC, they correspond to chronic stages (17).

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