

Progressive multifocal leukoencephalopathy presenting with confusion and behavioral disturbances in an HIV-negative patient

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Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system, caused by reactivation of the JC polyomavirus.¹⁻³ Although classically described in scenarios of severe immunosuppression, PML can on rare occasion affect patients with discrete, transient, or occult immunosuppression.^{1,3,4}

An HIV-negative 57-year-old man with history of alcoholic cirrhosis (Child-Pugh A) presented with confusion and behavioral disturbances, difficulty speaking, and gait instability that developed over the last two months. His altered behavior was characterized by psychomotor retardation and aggressivity. Neurological examination revealed mixed aphasia, right hemiparesis, and ipsilateral hemianopia. The patient regularly consumed alcohol and was not taking any medication.

Head computed tomography revealed confluent hypodensity in the white matter of the left frontal, parietal, and temporal lobes that extended to the contralateral parietal region through the splenium of the corpus callosum. Brain magnetic resonance imaging confirmed an extensive lesion involving the periventricular and subcortical white matter (including the subcortical U-fibers) of these regions that was hyperintense on T2-weighted images, hypointense on T1-weighted images (with no enhancement), and showed a typical rim of restricted diffusion along the active margins of inflammation, which was characterized by an increased signal in diffusion-weighted imaging with corresponding low values on the apparent diffusion coefficient map. Multiple T2-weighted images showed hyperintense punctate areas surrounding the lesion, as

well as in the right hemispheric white matter, consistent with a “Milky Way” pattern (Figure 1).

The patient had mild leukopenia (white blood cell count $3.3 \times 10^9/L$) that normalized two days later ($4.5 \times 10^9/L$). HIV serology was negative and the CD4+ T cell count was $0.230 \times 10^9/L$. Cerebrospinal fluid analysis showed slightly elevated proteins (0.64 g/L) and a normal cell count and glucose levels. Polymerase Chain Reaction analyses identified JC polyomavirus in the cerebrospinal fluid (3300 copies/mL). Based on these findings, PML was diagnosed, presumably linked to alcoholic cirrhosis, since other causes of immunosuppression were excluded.

Until recently, severe immunosuppression was considered an absolute requirement for developing PML. However, there are case reports of PML with less overt immunosuppression or with no documented immunosuppression.¹⁻⁴ In chronic diseases (i.e., alcoholic cirrhosis), transient or discrete failure in cellular immunity might be enough to promote JC polyomavirus reactivation.

A literature search yielded only 8 PML cases related to hepatic cirrhosis (3 with alcoholic etiology), including 1 woman and 7 men whose ages ranged from 41 to 64 years. Additional similarities to the present case included 3 cases with documented CD4+ lymphocytopenia or leucopenia and three descriptions of psychiatric symptomatology, which ranged from disorientation to severe mental confusion.^{2,4}

Clinical manifestations of PML are nonspecific. Patients frequently present with gradually worsening focal neurological deficits and may develop seizures, altered mental status, or cognitive deficits.^{1,2} Our patient presented with confusion and behavioral disturbances, indicating that psychiatric symptomatology may be the cornerstone of this condition's clinical presentation.

Definitive diagnosis of PML requires histopathological examination or the detection of JC polyomavirus in the cerebrospinal fluid of patients with consistent clinical and imaging manifestations.⁵ The prognosis is poor and there is no specific treatment; thus, it is important to identify and, if possible, treat the underlying cause of immunosuppression.²⁻⁴

In conclusion, PML has variable clinical manifestations and can affect patients with discrete or transient immunosuppression, making diagnosis particularly challenging. Although probably rare, it might be underdiagnosed in cases of cirrhosis. Therefore, early consideration of PML in cirrhotic patients with neurological and/or psychiatric manifestations is essential, along with adequate brain imaging and cerebrospinal fluid analysis.

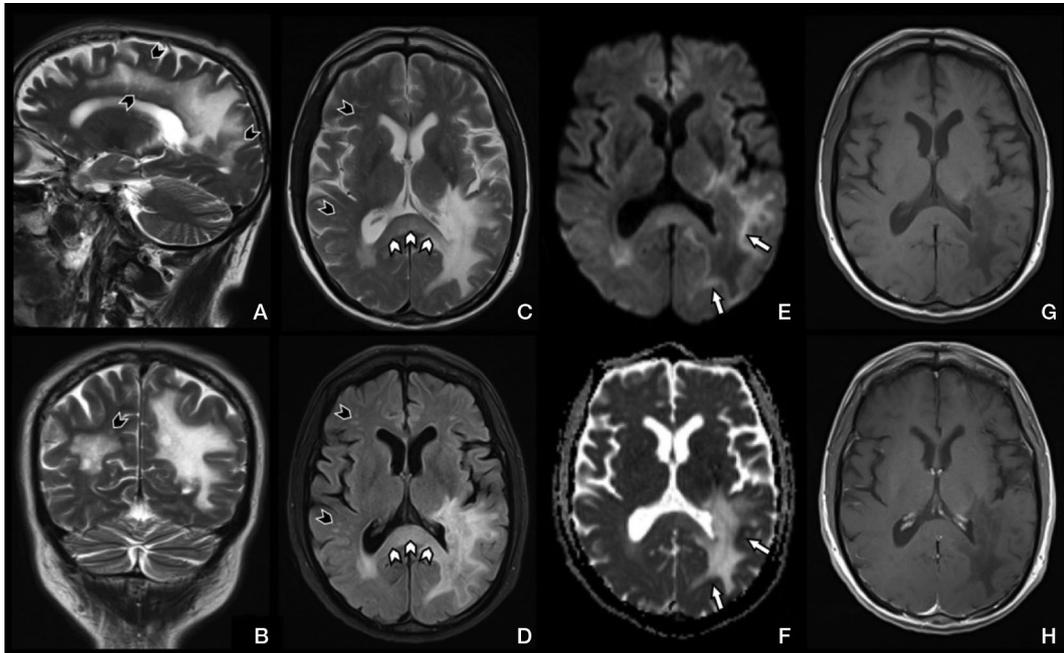


Figure 1 Typical findings of progressive multifocal leukoencephalopathy on magnetic resonance imaging of the brain. Sagittal (A), coronal (B), and axial (C) T2 turbo spin echo and fluid-attenuated inversion recovery. (D) Weighted images show an extensive hyperintense lesion involving periventricular and subcortical white matter of the left frontal, parietal, and temporal lobes (including the subcortical U-fibers), with a sharply demarcated peripheral border, sparing the cortex. It extended to the contralateral parietal region through the corpus callosum splenium, i.e., the “Barbell” sign (white arrowheads); note the absence of a relevant mass effect despite the size of the lesion. Axial diffusion-weighted imaging (E) and apparent diffusion coefficient mapping (F) show typical restricted diffusion along the peripheral advancing edge of the lesion (white arrows) and central facilitated diffusion. In T1-weighted images it is notably hypointense (G) with no enhancement in post-contrast sequence (H). Fluid-attenuated inversion recovery and T2-weighted images also showed multiple hyperintense punctate areas surrounding the lesion and white matter (black arrowheads) consistent with a “Milky Way” pattern in the right frontal and parietal lobes.

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Disclosure

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