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CASE REPORT

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Progressive multifocal leukoencephalopathy in an HIV patient: A case report and literature review

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Key Clinical Message

Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic infection of the brain caused by reactivation of the JC virus, which can lead to a lytic infection of oligodendrocytes. We report a patient with HIV who developed PML.

Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic infection of the brain caused by reactivation of the John Cunningham virus (JCV), which can lead to a lytic infection of oligodendrocytes. Herein, we report the case of a patient with HIV who developed PML that presented as a progressive disturbance of consciousness and movement. The patient's clinical symptoms progressively deteriorated, and positive JC viral DNA in his cerebrospinal fluid (CSF) helped us diagnose him with PML. Magnetic resonance imaging (MRI) showed multiple asymmetric subcortical and deep white-matter lesions. Although we administered immunoreconstructive therapy, the patient's condition gradually worsened. Therefore, we suggest that PML should be considered if such lesions are found in MRIs of HIV patients.

KEYWORDS

HIV, John Cunningham virus, next-generation sequencing, progressive multifocal leukoencephalopathy

1 | INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the central nervous system caused by the JC virus (JCV). This virus is a rare opportunistic infection that affects individuals with several conditions that cause immunosuppression.[1] The incidence of PML has increased steadily with the spread of the HIV/AIDS pandemic since the mid-1980s.[2] Currently, about 80% of PML patients have AIDS.[3] There is no specific treatment for PML; reconstitution of immunocompetence is crucial for patient survival. With the widespread implementation of highly active antiretroviral therapy (HAART), studies have shown that the incidence rates of PML have considerably declined.[4,5] However, the disease still carries a poor prognosis, with rapid progression and death usually occurring within 6 months.[6] Patients with HIV-associated PML are often left with neurological symptoms, even if they have received HAART. PML also has diverse clinical manifestations depending on the localization of the brain lesions. Therefore, it can be easily misdiagnosed as another HIV-related encephalopathy. Herein, we report the case of a patient with HIV who developed PML.

2 | CASE REPORT

A 34-year-old man who had been experiencing progressively slurred speech over the course of 1 month was admitted to the local hospital. He had a fever accompanied by dizziness and a headache, with a peak temperature of 38.0°C. The patient was confirmed to have an HIV infection (HIV-RNA level 1.89×10^5 copies/mL), and was transferred to another local hospital. Cranial magnetic resonance imaging (MRI) showed multiple abnormal signal intensities in the bilateral frontal–parietal lobes and left temporal lobe. Cerebrospinal fluid (CSF) cryptococcal antigen and mycobacterium DNA culture were negative. The patient was diagnosed as having toxoplasma encephalopathy and was started on an antiretroviral therapy (ART) regimen (tenofovir+lamivudine+dolutegravir). Because the patient had an allergic reaction to sulfa, the toxoplasma treatment regimen was switched to azithromycin and clindamycin. However, after 2 months of treatment, the patient developed a right limb movement disorder that gradually progressed to hemiplegia and was then referred to our hospital.

The patient's vital signs were stable on admission. He was slow to react, with a stiff expression. A physical examination showed the presence of scattered ecchymosis on his skin, covering his whole body. The patient's right limb muscle strength was 0 and his pathological signs were negative, but he did not cooperate with our sensory examination.

A laboratory examination showed that the patient's HIV-RNA level was 4.1×10^3 copies/mL, CD4 count was 41 cells/μL, and tumor markers were negative. The patient's blood was negative for any signs of bacterial, mycobacterial, or fungal infections. An MRI of the patient's brain showed patchy long T1 and long T2 signal shadows in the bilateral frontotemporal lobes, particularly in the left cerebral hemisphere. A T2 fluid-attenuated inversion recovery (FLAIR) sequence showed a high signal intensity and no obvious mass effect on T1-enhanced image (Figure 1). The patient had a fever during his hospitalization, with a peak body temperature of 38.7°C. As we could not entirely rule out tuberculous meningitis, a lumbar puncture was performed. CSF analyses showed normal levels of glucose, chloride, and protein, but the patient's nucleated cell count significantly increased to 9×10^6/L. CSF India-ink staining, acid-fast staining, and mycobacterium DNA culture tests were all negative. However, the patient's blood was also negative for antibodies to *T. gondii*.

On the basis of progressive neurologic manifestations, we began to suspect PML. Therefore, we performed two additional lumbar punctures. The CSF analyses were within normal ranges, but the CSF was found to be positive for JCV DNA using next-generation sequencing. Based on the results of the patient's clinical features, imaging findings, and

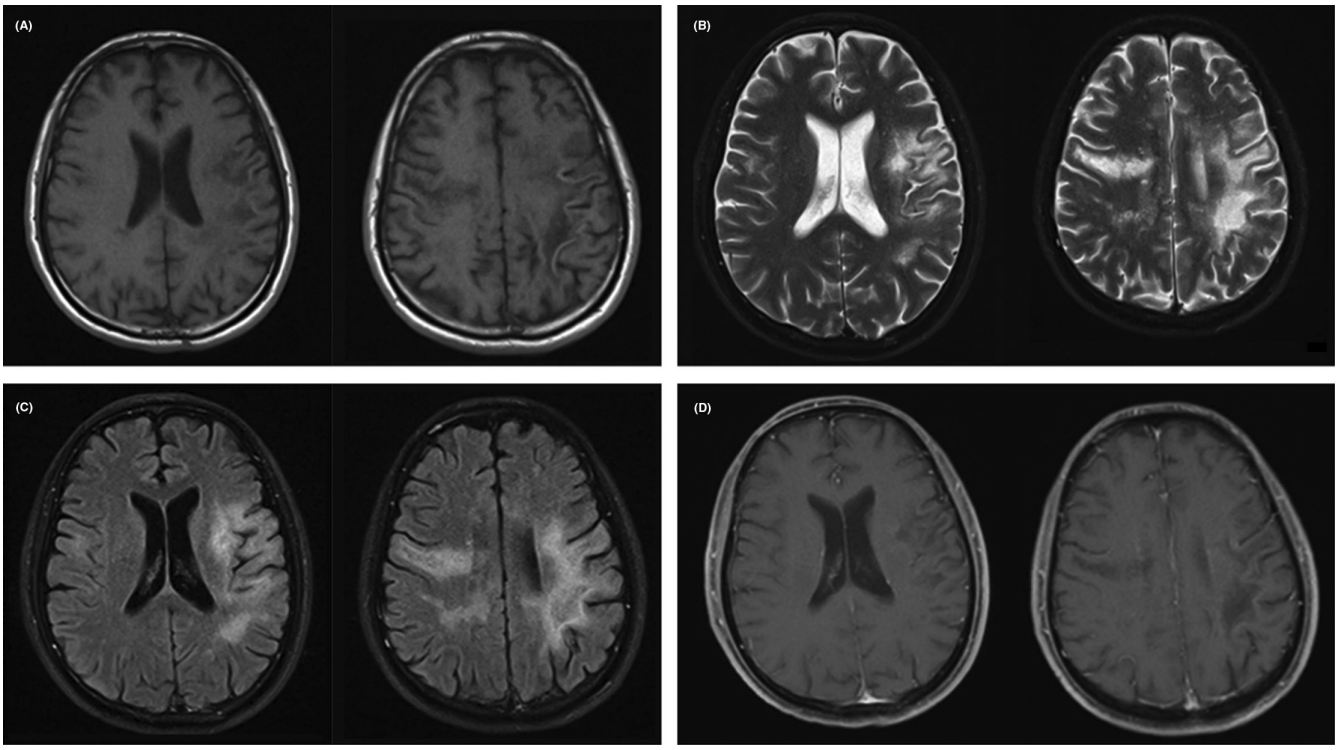

FIGURE 1 Magnetic resonance imaging results. T1-weighted images (A) showed multiple asymmetric patchy signal shadows on the subcortical bilateral frontal, temporal, and parietal lobes. These lesions were hyperintense on T2-weighted images (B) and T2 fluid-attenuated inversion recovery (FLAIR) images (C). No significant enhancement and mass effect was seen (D).

metagenomic next-generation sequencing (mNGS) testing, a diagnosis of HIV-related PML was made. In addition to the ART regimen (tenofovir-lamivudine-dolutegravir sodium, one tablet a day), human immunoglobulin and G-CSF (granulocyte colony-stimulating factor) were also used to support immunological reconstitution. However, the patient's symptoms continued to worsen. His family declined further tests and requested discharge. The patient then died 2 weeks following his discharge.

3 | DISCUSSION

We report the case of a patient with HIV who developed PML that presented as a progressive disturbance of consciousness and movement. Due to the patient's main clinical manifestations being fever, aphasia, and hemiplegia, differential diagnoses included cerebral toxoplasmosis and tubercular meningitis. Because the patient's clinical symptoms progressively deteriorated, the positive results of JCV DNA in his CSF by mNGS later led to a diagnosis of PML. Therefore, we suggest that when multiple asymmetric white-matter lesions are found in HIV patients, PML should be considered.

PML is a disease of the brain caused by the reactivation of JCV, leading to a lytic infection of oligodendrocytes.[7] Primary JCV infection mainly occurs in childhood and is asymptomatic, after which the virus remains latent, possibly in the lymphoid organs, neuronal tissues, and/or kidneys.[8] However, in cases of cellular immune deficiency, such as HIV/AIDS, viral reactivation can result in demyelination of the central nervous system (CNS).[9] The clinical presentation of PML varies depending on the affected cerebral areas and is nonspecific. It includes progressive weakness, speech disturbances, and visual field defects. The most common initial manifestations are gait disturbances and cognitive impairment.[10] Brain MRIs have important diagnostic value for PML. Single or multiple and round- or sector-shaped abnormal signals can be seen in the periventricular white matter or subcortical white matter, which can be fused with one other and distributed asymmetrically. T2-weighted images and FLAIR show hyperintense areas, while T1-weighted images show hypointense areas without mass and enhancement effects. Diffusion-weighted images often show lesions extending to the subcortical/juxtacortical white matter with peripheral patchy diffusion restriction, in such cases.[11] Although the gold standard for PML diagnosis is histopathological evidence, the diagnosis is usually suggested on MRI and confirmed by CSF PCR for JCV DNA.[12] For patients who cannot cooperate with a brain biopsy, the following three factors are required to confirm the diagnosis: the presence of progressive neurological symptoms, a head MRI revealing typical imaging PML features, and JCV DNA detected in the CSF by PCR.[13]

About 50% of patients with PML die within 6 months after clinical onset, and survivors are usually left with severe neurological sequelae.[14,15] As no specific treatment with proven efficacy is available, immune reconstitution remains the most effective strategy for treating PML. In patients with AIDS, ART should be initiated. If the patient is already receiving ART, the regimen should be altered to optimize immune recovery and normalize CD4 counts. Other therapeutic strategies that have been reported include recombinant IL-2, checkpoint inhibitors, and adoptive immunotherapy using virus-specific T cells.[16,17] However, it should be noted that all treatments aiming for immune reconstitution carry the risk of leading to immune reconstitution inflammatory syndrome (IRIS). IRIS is defined as unexplained neurological disorders or worsening of previously diagnosed PML attributable to the recovery of the immune system.[18] Some case reports have suggested that corticosteroids can be used early in cases of life-threatening PML-IRIS, but there is no clear consensus on the efficacy of this approach.[19]

Based on the above, the success of immune reconstitution depends on early diagnosis, limited disease progression, and rapid/effective immune repletion. Misdiagnosis and inappropriate treatment can aggravate the disease. In this case, an MRI scan of the patient showed a CNS disease. Differential diagnoses that we initially considered in this case were toxoplasma encephalopathy, cerebral tuberculosis, and PML. Their clinical features are all nonspecific and include headache, disturbance of consciousness, and mental/behavioral abnormalities. A presumptive diagnosis of cerebral toxoplasmosis in HIV-infected patients is based on multiple ring-enhancing lesions, particularly in the basal ganglia/thalami,[20] in imaging studies (CT/MRI) and a successful response within 2 weeks to specific treatment. A diagnosis of CNS tuberculosis is based on evidence of *Mycobacterium tuberculosis* in the CSF.[21] In such cases, contrast brain MRI scans often show enhancement of the meninges and the periphery of the tuberculoma, and are often accompanied by peripheral edema. In cases of tuberculosis, multifocal lesions with peripheral enhancement (ring-enhancing pattern) can be observed.[22] Slowly progressive focal neurological deficits with asymmetrical white matter abnormalities on MRI suggest PML. In addition, the lesions are non-enhancing and hyper-intense on T2-weighted MRI, without mass effect. In this case, our patient was diagnosed with toxoplasma encephalopathy at first. He was treated for 2 months for this condition without any improvement. His CSF showed no evidence of tuberculosis. A brain MRI showed multiple asymmetric lesions without significant

enhancement or mass effect. After we excluded the possibilities of toxoplasmosis encephalopathy or tuberculous meningitis, we suspected that AIDS-related PML was the most likely diagnosis. Ultimately, finding JCV in the patient's CSF confirmed our suspicion. However, when the patient experienced no apparent therapeutic benefits after 2 weeks of treatment for PML, other potential diagnoses should have been considered as well so as not to delay follow-up treatment.

In conclusion, for patients with AIDS with hemiplegia, aphasia, and other CNS dysfunctions, comprehensive examinations such as cranial MRI and CSF analysis should be performed as early as possible. When multiple asymmetric white matter lesions are found on MRI, and diffusion-weighted images demonstrate lesions extending to subcortical/juxtacortical white matter with peripheral patchy diffusion restriction, PML caused by HIV infection should be suspected in order to avoid misdiagnosis and missed diagnosis.

AUTHOR CONTRIBUTIONS

Ting Lei: Conceptualization; formal analysis; investigation; writing – original draft; writing – review and editing. **Ai Deng:** Investigation; writing – original draft; writing – review and editing. **Lianchi Li:** Data curation; investigation. **Ming Wang:** Funding acquisition; investigation; writing – original draft. **Dongbo Wu:** Funding acquisition; investigation; writing – original draft; writing – review and editing. **Taoyou Zhou:** Investigation; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

Personal data have been respected.

CONSENT STATEMENT

The written informed consent was obtained from the patient's family for the publication.

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