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Inflammatory Progressive Multifocal Leukoencephalopathy Without Immune Reconstitution in HIV: An Underrecognized Clinical Entity

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare, acquired immune deficiency syndrome (AIDS)-defining demyelinating disease caused by reactivation of the John Cunningham (JC) virus. It typically occurs in patients with advanced human immunodeficiency virus (HIV) infection and CD4 counts below 100 cells/mm^3.

This report describes an unusual case of microbiologically confirmed non-immune reconstitution inflammatory syndrome (non-IRIS) inflammatory PML in an antiretroviral therapy (ART)-naïve HIV patient with preserved immunity and an excellent long-term outcome. A male patient in his 40s presented with left-sided weakness, focal seizures, and a one-month history of headache. Brain magnetic resonance imaging (MRI) demonstrated multifocal asymmetric white matter lesions in the bilateral frontal and right temporoparietal regions, subcortical U-fibre involvement in the bilateral frontal lobes, subtle contrast enhancement, and hyperintense cortical signal (HCS), indicating inflammatory cortical involvement. Cerebrospinal fluid (CSF) analysis revealed a mildly elevated protein level, and JC virus polymerase chain reaction (PCR) was positive. HIV serology was positive, with a CD4 count of 212 cells/mm^3. The patient was initiated on ART with tenofovir, emtricitabine, and efavirenz, as well as antiepileptic medications. Over more than seven years of follow-up, the patient demonstrated significant neurological recovery and radiological improvement, with only occasional breakthrough seizures and residual frontotemporal atrophy on MRI. Although inflammatory MRI features such as enhancement and HCS are often associated with PML-IRIS, this patient had not received ART prior to presentation.

This case suggests the existence of a probable subset of non-IRIS inflammatory PML in ART-naïve HIV patients with relatively preserved CD4 counts. Early recognition of this atypical presentation is essential to avoid diagnostic delays and to facilitate timely ART initiation, which may improve long-term outcomes.

Categories: Neurology, HIV/AIDS, Infectious Disease
Keywords: demyelinating disease, human immunodeficiency virus (hiv), immune reconstitution inflammatory syndrome (iris), john cunningham virus (jcv), neuroimaging, non-iris pml in hiv, progressive multifocal leukoencephalopathy (pml)

Introduction

Progressive multifocal leukoencephalopathy (PML) is caused by the John Cunningham (JC) virus, a member of the polyomavirus family. This rare but severe neurological disorder is progressive and affects approximately 4% of individuals with human immunodeficiency virus type 1 (HIV-1). Consequently, PML is classified as an acquired immune deficiency syndrome (AIDS)-defining illness and typically occurs in advanced HIV infection when the CD4 count falls below 100 cells/mm^3 [1].

This report describes a case of PML confirmed by microbiological testing, which exhibited atypical immunological, radiological, and prognostic characteristics. The patient demonstrated a favourable long-term outcome, with subsequent clinical and radiological evaluations revealing only well-controlled scar epilepsy. In individuals with HIV infection, PML can manifest with diverse immunological and inflammatory phenotypes. Classical PML typically develops in severe immunosuppression and is marked by progressive demyelination from uncontrolled JC virus replication with minimal inflammation. In contrast, PML-associated immune reconstitution inflammatory syndrome (PML-IRIS) emerges following initiation of antiretroviral therapy (ART), when restored antiviral immunity induces inflammation in previously infected central nervous system (CNS) tissue. Clinically, this may present as neurological deterioration and, on imaging, as contrast enhancement, perilesional oedema, and mass effect. Notably, inflammatory features are not exclusive to ART-associated immune reconstitution. Inflammatory PML may also occur within a broader spectrum of JC virus-associated disease, exhibiting varying degrees of inflammation even in the absence of classical IRIS. Consequently, inflammatory neuroimaging findings in an ART-naïve patient

should prompt consideration of a non-IRIS inflammatory phenotype rather than automatic classification as PML-IRIS. In this case, the patient demonstrated radiological features suggestive of PML-IRIS despite having only recently initiated ART, indicating a non-IRIS inflammatory PML phenotype.

Case Presentation

A male patient in his 40s presented with a one-month history of left upper and lower limb weakness and right hemicranial headache. Twenty days prior, he experienced a single episode of left focal seizure. He also reported a brief episode of mild fever, which resolved with antipyretics. The patient was recently diagnosed with retroviral disease during admission to an outside hospital for these symptoms, but ART had not been initiated. On examination, he was haemodynamically stable, conscious, and oriented. The Glasgow Coma Scale (GCS) score was 15/15, with muscle strength graded as 4+/5 in the left upper limb and 2/5 in the left lower limb.

Investigations and treatment

Routine blood investigations were unremarkable, with the exception of positive HIV serology and a CD4 count of 212 cells per microlitre. Brain magnetic resonance imaging (MRI) demonstrated areas of altered signal intensity in the bilateral frontal, right basofrontal, right temporoparietal, and right capsuloganglionic regions, predominantly involving the superficial and deep white matter (Figure *1*). During the 2.5-3 years of follow-up after initiating ART, the patient showed sustained improvement in CD4 counts, which subsequently reached the normal reference range.

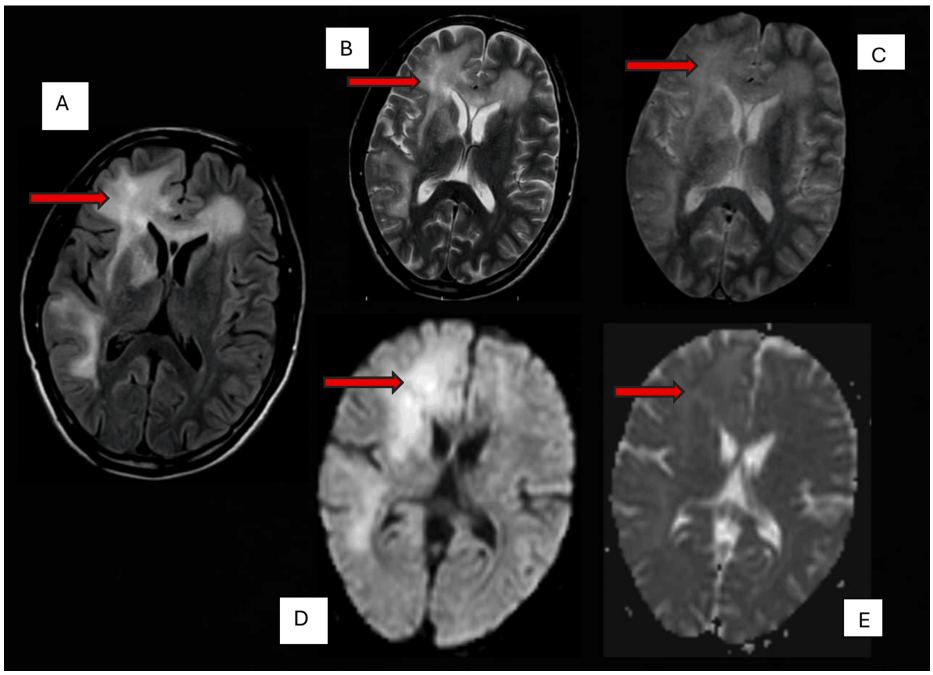


FIGURE 1: MRI Brain Images

A) FLAIR axial image shows bilateral frontal, right temporoparietal, and right capsuloganglionic region white matter hyperintense lesions.

B) T2 axial image demonstrates white matter lesions. Subcortical U-fibre involvement is seen in the right frontal region.

C) GRE axial images (T2 FFE) show absent blooming.

D) and E) DWI and ADC axial images show the lesions to be T2 shine-through.

FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; FFE, fast field echo; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; MRI, magnetic resonance imaging

Diffusion-weighted imaging (DWI) revealed T2 shine-through with patchy regions of free diffusion. These areas exhibited T1 hypointensity and were hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences. Gyriform T1 hyperintensity, consistent with hyperintense cortical signal (HCS), was primarily observed in the deeper cortex adjacent to the white matter lesion in the bilateral frontal lobes (Figure *2*). Gradient images showed no blooming. Additional findings included involvement of the genu of

the corpus callosum and patchy lesions in the high frontal subcortical white matter. The subcortical U-fibres in the bilateral frontal lobes were also affected (Figure *1*). Post-contrast imaging demonstrated subtle nodular enhancement along the lesion margins in the bilateral frontal lobes (Figure *2*). Cerebrospinal fluid (CSF) analysis showed only a mild elevation in protein (52 mg/dL). The CSF meningoencephalitis profile was positive for the JC virus. The patient had radiological features suggestive of PML-IRIS but was ART-naïve. Based on the above clinical context, a diagnosis of non-IRIS PML was made. ART was initiated using tenofovir, emtricitabine, and efavirenz. Additionally, antiseizure medications such as levetiracetam and clobazam were administered.

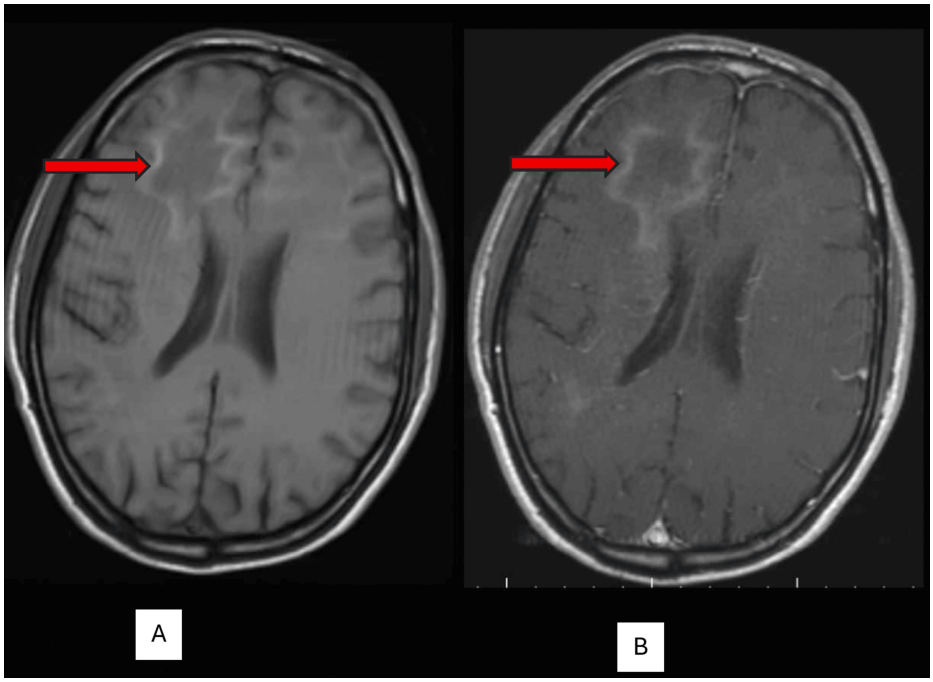


FIGURE 2: MRI Brain Images

T1WI pre-contrast (A) and T1WI post-contrast (B) axial images show hyperintense cortical signals in the bilateral frontal regions adjacent to subcortical white matter lesions. Post-contrast images demonstrate nodular enhancement.

MRI, magnetic resonance imaging

Outcome and follow-up

Over more than seven years of regular follow-up, the patient did not develop focal neurological deficits and resumed employment three months after discharge. In the following years, multiple short-term hospital admissions were required, each lasting one to two days, due to breakthrough seizures. These episodes were managed effectively through adjustments to anti-seizure medications. Follow-up MRI revealed atrophy in the frontotemporal regions and significant improvement in the lesions (Figure *3*). Mild enlargement of both lateral ventricles was noted, with more pronounced enlargement on the right side.

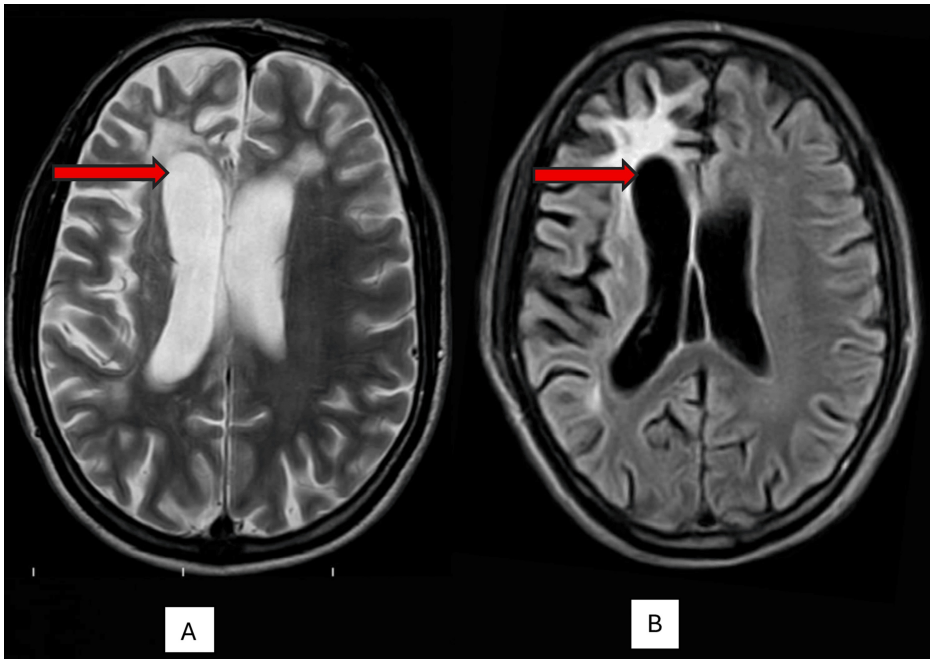


FIGURE 3: MRI Brain Images

Follow-up axial T2 (A) and FLAIR (B) MRI after 12 months showed atrophy in the involved areas, with ex vacuo dilatation of the bilateral lateral ventricles.

Mild enlargement of both lateral ventricles, with more pronounced enlargement on the right side.

FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

Discussion

HIV frequently affects the nervous system, making it a significant and serious target of HIV infection [1]. Neurological involvement occurs in up to 39% of individuals with HIV [2]. In some cases, neurological disease is the initial manifestation of symptomatic HIV infection and may also serve as a criterion for an AIDS diagnosis. PML is a rare but severe neurological disorder caused by the JC virus, a human polyomavirus first identified in 1958 in patients with lymphoproliferative disorders [3]. The JC virus is typically acquired asymptomatically during childhood or early adulthood and remains latent in lymphoid tissue and the kidneys in approximately 90% of the general population. The virus can reactivate in individuals with profound immunosuppression. Since the advent of HIV, AIDS has become the primary cause of PML [4]. Prior to the introduction of ART, up to 10% of HIV-infected individuals in developed countries developed PML [5]. Since ART became available, the incidence of PML has not declined substantially compared with other CNS diseases [5]. In India, two studies reported PML in 1.2% and 2.8% of HIV-positive patients [6,7], while a study in Ahmedabad documented an overall incidence of 3.5% [8]. PML is considered an AIDS-defining illness in approximately 1% to 3% of all HIV-positive individuals. It almost exclusively occurs in those with CD4 counts below 100 cells/mm^3, although rare cases have been observed with CD4 counts above 200 cells/mm^3. PML associated with AIDS is classified as either classic PML, which typically arises in the context of severe immunosuppression, or PML-IRIS. PML-IRIS is characterised by new or rapidly worsening PML shortly after initiation of highly active antiretroviral therapy (HAART), accompanied by evidence of immune recovery, such as a reduction in plasma HIV RNA by more than 1 log10 copies/mL and an increase in CD4 T cell count from baseline, as well as clinical features indicative of an infectious or inflammatory process.

The symptoms could not be attributed to a new infectious process or drug toxicity [7]. PML typically manifests as gradual disturbances in motor function, vision, or mental status. Seizures at disease onset occur in fewer than 9% of PML patients [9]; however, more than one-third of PML survivors experience seizures [10]. MRI is more sensitive than CT for detecting PML lesions. These lesions are generally solitary or multifocal, well-demarcated, and asymmetric within the white matter, appearing hyperintense on T2-weighted imaging (T2WI) and hypointense on T1-weighted images. Lesions are predominantly subcortical and often spare the periventricular white matter. Mass effect or contrast enhancement is typically absent. Subcortical U-fibre involvement may be observed. DWI may reveal peripheral restriction with central free diffusion. Magnetic resonance spectroscopy (MRS) demonstrates decreased N-acetylaspartate (NAA), increased choline, and elevated lactate levels. In a minority of PML patients, initiation of HAART can trigger an IRIS as immune function recovers. PML-IRIS is characterised by an acute inflammatory response and worsening neurological symptoms. Lesions associated with PML-IRIS may exhibit mass effect and

heterogeneous enhancement. HCS is observed in patients with cortical involvement [11], manifesting as gyriform T1 hyperintensity in the deeper cortical layers adjacent to white matter lesions. Although HCS resembles cortical laminar necrosis observed in chronic infarcts or other aetiologies, in this context, it results from direct involvement of the deeper cortical layers, leading to neuronal loss and cell death. This phenomenon is termed JC virus-associated focal leukocortical encephalitis (JCV FLE) [11]. The presence of HCS indicates a more pronounced inflammatory process, similar to PML-IRIS, and is associated with an increased risk of seizures. HCS on precontrast T1-weighted imaging has been described in various CNS conditions, most notably hypoxia/ischaemia, status epilepticus, hypoglycaemia, osmotic demyelination syndrome, and mitochondrial disorders. Less frequent associations include immunological disorders such as systemic lupus erythematosus (SLE), subacute sclerosing panencephalitis, and meningoencephalitis [12].

The CSF profile is generally unremarkable in both biochemical and cytological analyses. Polymerase chain reaction (PCR) detection of JC virus in CSF is considered diagnostic, with reported sensitivity between 72% and 92% and specificity between 92% and 100% [13]. ART has markedly improved clinical outcomes in PML among HIV-infected individuals, leading to extended periods of remission [14]. ART acts indirectly by increasing CD4 cell counts through its antiretroviral effects, thereby enhancing immune function. Prior to the introduction of ART, the mean survival for patients with PML was approximately three to four months. Currently, patients with suppressed plasma HIV viral loads due to ART often survive for years with stable neurological status [14].

A patient was newly diagnosed with HIV infection. Clinicians diagnosed PML based on clinical and radiological findings and confirmed it by detecting JC virus via PCR in the CSF. In this case, PML constituted an AIDS-defining diagnosis. The patient's CD4 count was greater than 200 cells/mm^3, a threshold at which PML is uncommon. The patient was ART-naïve and exhibited atypical inflammatory radiological features, including mass effect, subtle enhancement, and HCS, which are typically associated with PML-IRIS. Seizures at presentation indicated possible cortical involvement, further supported by HCS on MRI. The patient improved significantly and achieved long-term survival without notable morbidity. Previous studies have associated PML with the initial manifestation of AIDS, CD4 T lymphocyte counts greater than 200 cells/mm^3 at disease onset, lesion enhancement on imaging, and neurological recovery with favourable outcomes [9]. However, a case has been reported in the literature describing atypical inflammatory MRI features of PML in an ART-naïve HIV patient with a CD4 count above 200 cells/mm^3, resulting in a poor outcome [15]. Inflammatory features may be attributable to higher CD4 counts. Such cases may represent a distinct subset of PML observed exclusively in ART-naïve HIV patients with CD4 counts greater than 200 cells/mm^3 and inflammatory radiological features, which can be classified as non-IRIS inflammatory PML.

PML is an AIDS-defining illness that affects approximately 1% to 3% of HIV-positive individuals. It primarily occurs in those with severe immunosuppression, particularly when CD4 counts are below 100 cells/mm^3. PML is rare among patients with CD4 cell counts above 200 cells/mm^3.

In the context of AIDS, PML is classified as either classic PML, which typically develops during severe immunosuppression, or PML-IRIS. PML-IRIS refers to the new onset or rapid progression of PML soon after the initiation of HAART, accompanied by evidence of immune restoration. Immune restoration is indicated by a virological and immunological response, such as a reduction in plasma HIV RNA levels by more than 1 log10 copies/mL and an increase in CD4 T cell count from baseline, together with clinical symptoms and signs of an infectious or inflammatory process.

The symptoms could not be attributed to a new infectious process or drug toxicity [7]. PML typically presents with gradual disturbances in motor function, vision, or mental status. Seizures at disease onset are observed in fewer than 9% of PML patients [9], whereas more than one-third of PML survivors experience seizures [10]. MRI is more sensitive than computed tomography (CT) for detecting PML lesions. Solitary or multifocal, well-demarcated, asymmetric white matter lesions are frequently observed; these lesions appear hyperintense on T2WI and hypointense on T1-weighted images. The lesions are predominantly subcortical, with relative sparing of the periventricular white matter. Mass effect or contrast enhancement is generally absent. Subcortical U-fibre involvement may also be present. DWI may reveal peripheral restriction with central free diffusion. MRS typically demonstrates decreased NAA, increased choline, and elevated lactate levels. In a minority of PML patients, initiation of HAART may precipitate IRIS following immune recovery.

Conclusions

Among newly diagnosed ART-naïve HIV patients with relatively preserved CD4 cell counts, clinicians should remain vigilant for atypical clinical and radiological manifestations of non-IRIS and inflammatory PML. Prompt recognition of these cases is essential to minimise unnecessary diagnostic procedures and reduce delays in initiating appropriate treatment.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the

work.

Concept and design: Dipin Dileep, Aumir Moin, Vijay Halagappanavar Vamadevappa, Shraddha Kedlaya K

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Drafting of the manuscript: Dipin Dileep, Aumir Moin, Vijay Halagappanavar Vamadevappa, Shraddha Kedlaya K

Critical review of the manuscript for important intellectual content: Dipin Dileep, Aumir Moin, Vijay Halagappanavar Vamadevappa, Shraddha Kedlaya K

Supervision: Dipin Dileep, Aumir Moin, Vijay Halagappanavar Vamadevappa, Shraddha Kedlaya K

Disclosures

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