

Neuroimaging Insights Into Early Stages of HIV-Progressive Multifocal Leukoencephalopathy: A Case Report

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ABSTRACT: This report aims to enhance the understanding of early longitudinal neuroimaging features of progressive multifocal leukoencephalopathy (PML) in human immunodeficiency virus (HIV). Neuroimaging has become crucial in the diagnosis and early recognition of PML. Recognition of magnetic resonance imaging (MRI) features in the early stages of PML is paramount to avoid misdiagnosis and facilitate the delivery of treatments aimed at reducing disease progression. A 49-year-old white man with HIV presented with 4-month progressive left-sided weakness. Neurological examination revealed mild cognitive impairment, left-sided hemiparesis, and somatosense impairment to all modalities. Brain MRI revealed a punctate pattern with innumerable T2-FLAIR (fluid attenuated inversion recovery) hyperintensities in the cortex, brainstem, cerebellum, subcortical, and periventricular areas. Susceptibility-weighted imaging (SWI) revealed hypointensities involving subcortical U-fibers and cortical architecture. A comprehensive diagnostic evaluation was inconclusive. John Cunningham virus (JCV) PCR in cerebrospinal fluid (CSF) was indeterminate. He was started on antiretroviral therapy. Repeat brain MRI performed 1.5 months later, in the setting of further neurological decline, demonstrated progression of the T2-hyperintensities into a large confluent white matter lesion in the right frontoparietal lobe. Despite an indeterminate JCV PCR, the appearance and characteristic progression of the lesions in successive imaging in the setting of severe immunosuppression, with extensive negative infectious workup, was indicative of PML. This clinical experience illustrates unique neuroimaging features of HIV-PML in early stages and its progression over time. It especially highlights the relevance of the SWI sequence in the diagnosis and features observed with disease evolution. Short-term imaging follow-up may assist with the recognition of MRI features consistent with the biology of the infection.

KEYWORDS: Progressive multifocal leukoencephalopathy, HIV, punctate pattern, SWI, neuroimaging, neuroinfectious disease

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) that occurs mainly in immunocompromised patients. Especially, those with impaired cellular mediated immune response such as lymphoproliferative diseases or patients receiving monoclonal antibodies therapies such as natalizumab in Multiple Sclerosis (MS), and human immunodeficiency virus (HIV).¹ Progressive multifocal leukoencephalopathy is caused by John Cunningham virus (JCV) reactivation and replication within the oligodendrocytes, astrocytes, and occasionally neurons.^{2,3} This leads to destruction of these cells by direct effects of JCV or due to the viral recognition by CD4⁺ and CD8⁺ cytotoxic lymphocytes causing destruction of these cells, ultimately leading to demyelination.²

Most commonly, HIV-PML occurs in acquired immunodeficiency syndrome (AIDS) state, when CD4⁺ counts fall below 100.⁴ Nevertheless, PML is one of the few opportunistic infections that can also develop with much higher CD4⁺ counts.⁵ Furthermore, it can also occur in the setting of immune reconstitution inflammatory syndrome (IRIS) after starting antiretroviral therapy (ART). The PML-IRIS can also develop in patients discontinuing immunosuppressive medications,

such as MS patients discontinuing natalizumab.⁶ The PML-IRIS consists on paradoxical worsening of neurological symptoms in the setting of recovery of the immune system.^{7,8}

PML infection has usually a devastating course with a progressive neurological decline, and it is notorious for cognitive and motor deficits.^{9,10} Magnetic resonance imaging (MRI) has become crucial in diagnosing PML as it can detect the presence of disease in the asymptomatic phase. For this reason, being able to recognize MRI changes in early stages of PML is essential. Progressive multifocal leukoencephalopathy lesions are characteristic for evolving over time and this occurs for 2 main reasons, either progression of the infection itself or development of immune response against JCV. Here we describe the case of an HIV-positive patient who presented with PML in early stages, and brain imaging revealed an uncommon phenotype.

Case Report

A 49-year-old right-handed Caucasian man with a recent diagnosis of HIV presented with a 4-month history of progressive left-sided arm and leg weakness. Patient was diagnosed with HIV 2 months prior to this visit (CD4⁺ count: 270 cells/mm³) but he refused to start ART. At that time, he was also diagnosed with latent syphilis (rapid plasma regain [RPR]



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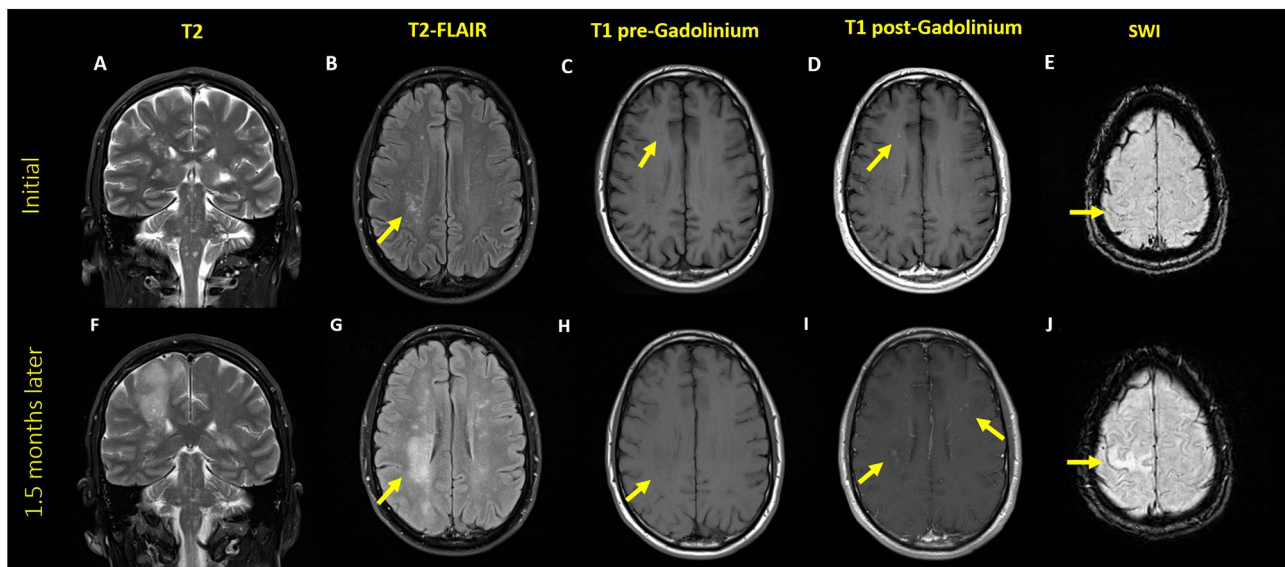


Figure 1. Neuroimaging changes in PML: (A and B) Multiple T2-hyperintensities revealing a punctate pattern. (C and D) Pre- and post-gadolinium image files revealing a punctate focus of enhancement. (E) Hypointense region observed near the region of abnormality on SWI. (F and G) Interval progression of the punctate lesions evolving into a confluent large white matter lesion. (H and I) Pre- and post-gadolinium features demonstrating increased punctate enhancement in the setting of PML-IRIS after ART initiation. (J) SWI sequence demonstrating a hypointense rim revealing the involvement of the subcortical U-fibers and cortical architecture. ART indicates antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome; PML, progressive multifocal leukoencephalopathy; SWI, susceptibility-weighted imaging.

1:32), and he received a 14-day course of IV penicillin. Neurological examination revealed mild cognitive impairment, left-sided spastic hemiparesis sparing the face with intact strength on the right side, impaired left-sided primary somatosense to temperature, pinprick, and vibration at the distal joint of the great toe. Appendicular ataxia (left more prominent than right) was also observed. Brain MRI revealed a punctate pattern with innumerable T2-FLAIR (fluid attenuated inversion recovery) hyperintensities in the cortex, brainstem, cerebellum, subcortical, and periventricular areas (Figure 1A and B). These areas also demonstrated hyperintensity on diffusion weighted imaging (DWI) and few of them revealing T2-shine through on the apparent diffusion coefficient (ADC) sequence. Around the periventricular region, there were areas of punctate enhancement (Figure 1C and D). The right hemisphere demonstrated a higher lesion burden than the left. A hypointense rim involving the subcortical U-fibers on susceptibility-weighted imaging (SWI) was also observed (Figure 1E). Cervical and thoracic spine MRI were unremarkable. Serum demonstrated a CD4⁺ count of 197 cells/mm³ with a HIV viral load of 23 290 copies/mL and RPR titer of 1:256. The results from a comprehensive diagnostic evaluation were inconclusive. Lumbar puncture revealed 9 nuclear cells/mm³ (95% lymphocytic), 9 red blood cells/mm³, protein of 86 mg/dL, and glucose of 54 mg/dL (serum 100 mg/dL). Infectious investigation of the CSF was significant for positive Epstein-Barr virus (EBV) PCR (483 copies/mL) and indeterminate for JC virus (JCV) PCR. Cytology revealed no abnormal cells and flow cytometry did not show evidence of non-Hodgkin's lymphoma. He was started on ART. He received a 14-day course

of IV penicillin, given the elevated RPR titer, although it is possible that was still elevated due to inappropriate response to the original course of penicillin, it was most likely thought to be elevated due to recent syphilis treatment completion given the negative VDRL in CSF. He was also started on acyclovir but due to the lack of response and negative infectious work up, it was discontinued. The presence of EBV was thought to be a concomitant opportunistic colonization as prior studies have described in severely immunosuppressed HIV patients.¹¹ Brain biopsy was not performed due to the non-targetable lesions. Single-photon emission computed tomography/computed tomography (SPECT/CT) brain was negative for Thallium avid-lymphoma. Repeat brain MRI (1½ months later) performed in the setting of further neurological decline demonstrated interval progression of the T2-FLAIR hyperintensities involving the subcortical U-fibers and extending to the corona radiata, with evolution into a large confluent white matter lesion in the right frontoparietal lobe (Figure 1F and G). There was also increased patchy enhancement along these FLAIR hyperintensities (Figure 1H and I). Ultimately, his neurological deterioration stabilized, and he transitioned to acute in-patient rehabilitation. In a recent 3-month follow-up visit, he still demonstrated left-sided arm and leg spastic hemiparesis although he was able to ambulate with a cane.

The appearance and characteristic progression of the lesions in successive imaging in the setting of severe immunosuppression, with extensive negative infectious workup, was indicative of PML. Cytomegalovirus encephalitis, toxoplasmosis, and fungal infections such as cryptococcosis, candida, and aspergillosis were ruled out with a negative serological tests. Other

diagnosis in the differential were considered such as HIV encephalopathy and primary CNS lymphoma. However, despite an indeterminate JCV PCR, this presentation was radiologically and clinically consistent with PML.

Discussion

This clinical presentation describes a severely immunocompromised HIV patient presenting with PML. Early stages of PML exhibit distinct neuroimaging features such as punctate pattern, increased signal in DWI along with T1-hypointensities, and involvement of the subcortical U-fibers.^{2,12-14} Generally, these early structural changes are asymptomatic. Therefore, being able to recognize the early MRI findings associated with PML is of great importance to avoid misdiagnosis and facilitate the delivery of treatments aimed at reducing disease progression.¹⁵ This is particularly important in MS patients who are on natalizumab as serial MRI monitoring has led to an increase in the recognition of PML prior to symptom development therefore allowing the earlier administration of treatment. In contrast with the MS population, HIV-PML patients are usually diagnosed when the disease is advanced; therefore, there is a paucity of literature regarding early PML stages in HIV.^{11,16,17}

Punctate pattern was first described in MS patients on natalizumab (NTZ-PML).¹⁸ It consists of several punctate multifocal hyperintense T2-FLAIR lesions that can be supra- or infratentorial. They can appear next to a larger PML lesion, displaying the described Milky Way appearance.¹⁹ In certain cases, some of these punctate lesions can be enhancing which indicates active inflammation, and it is more commonly seen in PML-IRIS.¹⁸ Interestingly, histologic examination of these enhancing lesions has shown perivascular infiltration with CD8+ lymphocytes.^{13,15}

In addition, this case highlights the importance of the SWI sequence in recognizing features suggestive of PML. Susceptibility-weighted imaging revealed a characteristic hypointense rim. This rim was observed on the cortical side and not in the center of the PML lesions. It exclusively affected the U-fibers and it followed the cortical architecture. This finding did not correlate with contrast enhancement and with the DWI sequence. In the subsequent MRI (Figure 1J), the rim increased in thickness, but continued to be limited to the gyral architecture. In PML, this neuroimaging feature has been proposed as a prognostic biomarker for long-term survival as it has postulated to be an end-point of the inflammatory process.¹⁴ Interestingly, this rim has also been observed in chronic cerebral infarction and encephalitis.²⁰ The cause of this rim remains unresolved although it has been hypothesized to be secondary to iron deposition within macrophages.¹⁴ Oligodendrocyte death due to JCV infection causes iron release which subsequently generates reactive oxygen species, ultimately leading to demyelination and cell death of the astrocytes and neurons.²¹

In this patient, the diagnoses of PML was reached after a negative extensive infectious work up and a repeated brain MRI revealing the progression of the punctate lesions into

the more classic large confluent white matter lesion. It is important to note that JCV PCR in CSF has a sensitivity of approximately 80%.²² Biopsy-proven PML has also been observed in the setting of a negative JCV PCR.²³ Consequently, the correct interpretation of brain MRI findings of early stages of PML becomes even more relevant in this case.

Conclusions

Improving the understanding of PML neuroimaging features from these experiences may provide further insights into the biology of this disease. This clinical experience presented here demonstrates neuroimaging findings in early stages of PML and the subsequent evolution of these changes overtime. In addition, this report provides additional evidence for the relevance of the SWI sequence as a meaningful imaging marker in PML. Furthermore, the rapid progression of these MRI findings in the repeat imaging suggests that when diagnosis is non-definitive, short-term imaging follow-up is paramount.

Author Contributions

NGC gathered data and drafted the manuscript for intellectual content. JSL revised the manuscript for intellectual content. DTO revised the manuscript for intellectual content.

Informed Consent

The patient described here provided written informed consent for the publication of this case report.

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