

Progressive Multifocal Leukoencephalopathy and Immune Reconstitution Inflammatory Syndrome in an HIV Patient with Favorable Outcome Using Combination of Antiretroviral Therapy and Systemic Corticosteroids: A Case Report

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a devastating, progressive disease characterized by multifocal demyelination. Reactivation of a polyomavirus, JC virus (JCV), is a major cause of PML, inducing a non-inflammatory, lytic reaction, demyelination, necrosis, and cell death. Immune reconstitution inflammatory syndrome associated with progressive multifocal leukoencephalopathy (PML-IRIS), a paradoxical neurological deterioration, despite dramatic improvement in CD4 and viral load, has been reported following initiation of "Highly active antiretroviral therapy" (HAART) in 18% of patients. Patients present with visual deficits (45%), decline in cognitive skills, confusion, personality change (38%); weakness, including hemi- or monoparesis; and ataxia and seizures (20%). Some patients develop PML during immune reconstitution. Survival is very poor in patients with CD4+ T-cell count < 200 cells/mm³. No definitive treatment has been established. Here we describe the diagnosis and management of a 50-year-old Afro-Caribbean man who was found to have AIDS, treated with antiretroviral regimen but soon develop worsening of neurological symptoms and poor functional performance status. He was found to have PML on brain MRI and JC virus on CSF fluid analysis. His course was further complicated with immune reconstitution inflammatory syndrome (IRIS). Patient responded dramatically to HAART with good CNS penetration along with adjuvant corticosteroids treatment. After 24-month follow-up, patient is alive with stable disease.

Keywords: Immune reconstitution inflammatory syndrome (IRIS), Progressive multifocal leukoencephalopathy (PML), corticosteroids, Highly Active Antiretroviral Therapy (HAART)

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare and devastating progressive disease characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the brain with cytologic alterations in both astrocytes and oligodendrocytes that typically result in severe neurological impairment and death [1]. Studies have confirmed reactivation of a polyomavirus, JC virus (JCV), is a major cause of PML. JCV infects oligodendrocytes and astrocytes in the CNS, inducing a non-inflammatory lytic reaction leading to demyelination, necrosis, and cell death [2]. PML is most common in patients with HIV infection, lymphoma or leukemia, carcinoma, sarcoidosis, tuberculosis, or pharmacologic immunosuppression following organ transplantation, and rare in those with normal immune function [3]. In the era of combined highly active antiretroviral therapy, (PML) continues to occur in 5% of patients with AIDS [4]. This diagnosis carries significantly high morbidity and mortality [1]. Despite recent advances in antiretroviral therapy, PML may worsen with effective treatment of HIV. This phenomenon, also seen with other opportunistic infections, is called P (PML) - immune reconstitution inflammatory syndrome (IRIS) [5-7]. IRIS is characterized by replenishment of immune cells depleted by HIV infection, circulating of immune cells situated in compartments of the immune system, regeneration of lymphoid organs and recovery of pathogen or antigen-specific T, B, and NK response, diversity of response and regulation of the reconstituted immune system [6]. Riedel DJ et al. [7] described immune reconstitution inflammatory syndrome in the CNS as a paradoxical neurological deterioration, despite dramatic improvements in HIV viral load and CD4⁺ T-cell counts

following initiation of HAART therapy in some of their patients. This phenomenon was observed in up to 18% of HIV-infected patients with PML [8]. Other organisms like mycobacteria, cryptococci, herpesvirus, cytomegalovirus, and JCV are increasingly being recognized as a cause of HIV-associated IRIS [8]. Patients often present with visual deficits (45%), decline in cognitive skills like dementia, confusion, personality change (38%); weakness, including hemi- or monoparesis; and ataxia and seizures (20%) [1,9].

When patients with PML have MRI imaging, typically PML lesions are non-enhancing and hypointense on T1 imaging and hyper intense on T2 W and FLAIR sequences without mass effect or displacement of normal structures however, if PML is associated with IRIS, patients can have contrast enhancement on T1 associated with mass effect or edema. Interestingly, Tan et al. [5] described a favorable outcome in patients who develop IRIS on pre-existing PML compared to patients who

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develop PML-IRIS simultaneously. Table 1 describes factors associated with outcome of PML-IRIS.

To date, there are no evidence-based guidelines for the management of PML-IRIS. Here we report a case of patients with severe AIDS, worsening of neurological symptoms and poor functional performance status who responded dramatically to new HAART therapy along with adjuvant systemic corticosteroids.

Observation

A 50-year-old African American man of Caribbean descent initially presented with progressive shortness of breath, fever and cough lasting for 2 weeks. He had no neurological symptoms or signs at that period of time. He was diagnosed with HIV/AIDS (CD4⁺ T-cell count: 54 cells/mm³) with viral load 82,273 copies/mL (branched-DNA tecquine, Seimens etc...) and *Pneumocystis jiroveci pneumonia* (PCP). He was treated with sulfamethoxazole-trimethoprim and prednisone. After completion of twenty-one day course, he was finally started on HAART regimen with emtricitabine-tenofovir, atazanavir, ritonavir and raltegravir. The regimen was justified because of concerned about viral resistance due to his long-time female sexual partner, who had been non-adherent to therapy, had died of AIDS complication. Her genotype demonstrated an M184V mutation two years prior to her demise.

Two months later he presented with blurred vision, headache, and progressive involuntary hand movements more marked in the left hand, difficulty in walking and difficulty in swallowing food. Examination revealed a disconjugate gaze, diplopia, choreoathetoid movement in his left hand and unsteady gait. Examination of the retina showed no evidence of CMV-associated retinitis. Because of dysphagia, upper gastrointestinal endoscopy was performed. No esophageal pathology was identified.

In view of his worsening of neurological findings, an MRI was performed. It showed patchy enhancement and few non-enhancing lesions in the cerebellum on T1 imaging and diffuse extensive T2-FLAIR abnormalities in the pons, bilateral periventricular white matter, at the junction of the right thalamus and internal capsule, and left parietal lobe (Figure 1). The CD4⁺ cell count had increased from 54 to 149 cells/mm³, and her HIV-1 viral load decreased from 82,273 to <75 c/mL (undetectable viral load) (Polymerase chain reaction (PCR) using the Versant (R) HIV-1 RNA 3.0 Assay (bDNA) kit by Siemens at Quest Diagnostic Laboratories, Nichols Chantilly, 14225 Newbrook Drive, Chantilly, VA 22021). Progressive multifocal leukoencephalopathy with immune reconstitution inflammatory syndrome (PML-IRIS) was diagnosed. Table 1 describes the laboratory values at the time of presentation.

Analysis of cerebrospinal fluid (CSF) showed clear, colorless fluid with normal WBC count (4 cells/mm³), 0 RBC/mm³, a normal glucose level of 56 mg/dL, and a normal protein level of 46 mg/dL. CSF viral polymerase chain reaction (PCR) was positive for JC-virus (JCV) and negative for herpes-simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Toxoplasma gondii and test for Human T-lymphotropic virus (HTLV) antibody. Staining for acid-fast bacilli (AFB) was equivocally positive (per 100 high power-fields (HPF). PCR for *M. tuberculosis* was undetected. Because of the equivocal AFB stain, the patient was treated initially with high-dose intravenous methylprednisolone with anti-tuberculous. Anti-tuberculosis medications were later discontinued once PCR for *M. tuberculosis* was undetected (Table 2). The HAART regimen was also changed. The choice of HAART combination (Zidovudine-Lamivudine, Nevirapine) was selected

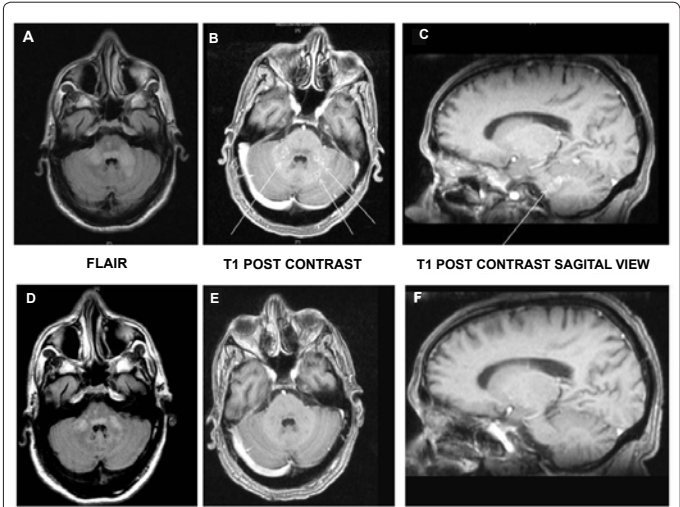


Figure 1: (A-C) (Prior Treatment) Axial fluid-attenuated inversion recover (FLAIR) (A), T1 post contrast (Axial (B) and Sagittal view (C)) performed at 9 month reveal diffuse white matter changes in the cerebellum prior to the treatment with contrast enhancing lesions hyperintense in the cerebellum and hypointense in the pons. Figure D-E (Post treatment) marked decrease in FLAIR abnormalities and resolution of contrast enhancement to hypointense lesion in the cerebellum.

Blood	Patient Values	Reference Range
Red blood cell count	4.34	4.20-5.8 10 ⁶ /L
Hemoglobin	14.3	12.3-17.3 g/dl
White blood cell count	5.4	4.00-11.00 10 ⁹ /L
Platelets	212	130-450 10 ⁹ /L
ALT	44	21-72 U/L
AST	48	17-59 U/L
Alkaline Phosphatase	124	38-126 U/L
Serology		
RPR	Non-Reactive	
Serum Cryptococcal	Non-Reactive	

Table 1: Laboratory values at the time of presentation.

CSF		Reference Range
Appearance	Clear, Colorless	
Xanthochromia	Negative	
CSF WBC	4	0.0-5.0 cells/uL
CSF RBC	0.0	No RBC
CSF Glucose	56	40-80 mg/dl
CSF Protein	46	50-54 mg/dl
HSV 1 & 2 -DNA PCR	Not detected	Not detected
Acid Fast Bacilli	2	Not detected
	per 100 high-power fields (HPF)	
Mycobacterium tuberculosis PCR	Negative	Negative

Table 2: Cerebrospinal Fluid Analysis.

to enhance central nervous system penetration. Given the rarity of the manifestation of PML-IRIS together with no effective treatment, we decided to continue steroids in our patient in view of few clinical studies and isolated case report available in the literature which have shown impressive results and prolong survival in these patients. MRI also demonstrated multiple lesions including cerebellar white matter, right thalamus, left parietal lobe, right putamen, right subinsular

Factors predicting good outcome	Factors present in our patient
At diagnosis	
Non-progressive".Neurological symptoms [5]	No
CD4+ T-cell count >100 cells/mm ³	No
Gadolinium Contrast enhancement on MRI [5]	Yes
Early Interventions and response	
Earlier use of steroids after the recognition of IRIS [5]	Yes
Radiological improvement within 6 month after introduction of HAART [17]	Yes
Factors predicting poor outcome	
Progressive Neurological symptoms [5]	Yes
Worsening of preexisting PML [5]	Yes
Late use of steroids in the course of IRIS [5]	No
Lesion load on PML-IRIS MRI >2 [5]	Our patient had diffused multiple lesions (Lesion load 51) on MRI including cerebellar white matter, right thalamus, left parietal lobe, right putamen, right subinsular region, right posterior frontal lobe and bilateral periventricular white matter. Post treatment lesion load decreased to 25.

Table 3: Factors affecting clinical outcome in PML-IRIS in HIV patients.

region, right posterior frontal lobe and bilateral periventricular white matter along with worsening neurological symptom. In view of these rational we continue steroid therapy in our patient.

Patient was maintained on prednisone 10 mg, orally, daily. MRI performed after three month and subsequently after nine months revealed disappearance of contrast enhancement in the cerebellum, marked decrease in T2-FLAIR abnormalities in the brainstem, left cerebral peduncle and thalamus (Figure 1). At 24 months from presentation, disconjugate gaze and dysphagia have resolved. Fine motor control was improved. Athetoid movements are stabilized with anticonvulsants.

Discussion

We describe the successful clinical management in an AIDS patient who presented with progressive multifocal leukoencephalopathy complicated by immune reconstitution inflammatory syndrome. IRIS is usually explained by reconstitution of a compromised immune system, followed by a strong immune response and inflammation. This may lead to a paradoxical clinical worsening of an appropriately treated disease. French et al. [9] described the proposed criteria for IRIS which includes major criteria: atypical presentation of opportunistic infection in patients responding to antiretroviral therapy (ARV) and decrease in plasma HIV RNA level by >1 log₁₀ copies/ml and minor criteria includes increased blood CD4 T-cell count after ARV as seen in our patient. Restoration of immune function by HAART is the only effective therapy for PML in patients with HIV/AIDS. However, survival is usually poor despite HAART therapy [5]. Since PML-IRIS occurs due to an imbalance of CD8⁺/CD4⁺ T cells. Furthermore, HIV gene products, such as Tat, may be able to transactivate the JC viral promoter directly, contributing to pathogenesis of PML, beyond the immunosuppression. Thus, HAART with good penetration in CNS and steroids theoretically may improve the PML-IRIS [6]. Letendre S et al. [10] validated the results that poorer penetration of ARV drugs into the CNS appears to allow continued HIV replication in the CNS as indicated by higher CSF HIV viral loads.

Individual cases of arrested progression of PML after starting

HAART suggest that immune reconstitution is beneficial to controlling JCV presumably because of cellular immune response against JCV antigens, but other cases of PML have progressed in spite of HAART. Imaging studies demonstrate inflammatory changes and brain biopsies have shown inflammatory cell infiltrates with prominence of CD8 T cells [6,7,11]. Since these findings suggest that the inflammation reflects restoration of a CD8 T-cell response against JCV antigens, exacerbations and first presentations of PML in patients on antiretroviral therapy can be considered paradoxical and unmasking forms of IRIS, respectively. Some studies call the paradoxical form PML-delayed IRIS and the unmasking form PML-simultaneous IRIS [11]. Several factors predictive of development of IRIS include initiation of HAART, active or subclinical opportunistic infection at initiation of HAART, low CD4 count (<100 cells/mm³), high CD8 cell count and a rapid decreased plasma viral load [5,6].

In our case, we have noticed low CD4 count (CD4 54/mm³), rapid decline in viral load (undetectable, <75), and high CD8 count (1,414/mm³) were the early predictors for IRIS. However, there are several factors classified as good and poor prognostic factors on the basis of anecdotal data. In a retrospective analysis of PML-IRIS cases conducted by Tan et al. [5] patients who developed IRIS superimposed on PML have a worse outcome compared to patients who develop PML-IRIS simultaneously. However, there is still considerable controversy with regard to other factors affecting the outcome in PML-IRIS. Table 3 described factors predicting good versus bad outcome in these patients.

It is interesting to note that classical PML lesions lack gadolinium contrast enhancement on an MRI however, the presence of enhancement is suggestive of an inflammatory response with breakdown of the blood-brain barrier. Therefore, enhancement with gadolinium may be a surrogate marker for IRIS. Tan et al. [5] found that only half of their patients with CNS-IRIS demonstrated contrast enhancement on MRI. Possibly the absence of contrast enhancement delayed the diagnosis of PML-IRIS. This would represent a lead-time bias and cause them to interpret the lack of enhancement as predicting a poor prognosis. In a retrospective review on 87 patients diagnosed with PML, 27 of which had a syndrome consistent with IRIS found poor prognosis in patients with gadolinium enhancement [12]. Another multicenter observational study cohort study on 61 patients found similar mortality in PML patients with or without IRIS [13].

Although, there are no randomized trials on the use of steroids in the management of PML-IRIS, some authors advocate use of steroids in IRIS when there is major neurologic worsening, clinical or radiologic evidence of swelling, mass effect, or brain herniation [5,6]. In a retrospective study conducted by Tan et al. [5] retrospective review showed that early and prolonged use of steroids correlated with improved survival. Berger J [14] has suggested that the role of corticosteroid therapy for PML-IRIS should be analyzed with foreknowledge of the critical contribution of the immune response to JC virus in controlling PML. Travis et al. [15] reported the successful management of pulsed methylprednisolone in patient presented with PML and IRIS together. Other studies have reported fulminant inflammatory leukoencephalopathy associated with HAART induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy despite high doses of corticosteroids [16].

We believe that the striking clinical and neuroradiological improvement in our patient can be attributed to the restoration of effective cell-mediated immunity secondary to the combination of HAART as well as corticosteroids. While HAART has no direct effect

on JCV replication, which is one of the main features of PML-IRIS, the reactivation of JCV- immune mediated injury as well as the immune-mediated injury of IRIS can be suppressed with corticosteroids. This immune modulation is managed concomitantly with achieving reduction of HIV viral load using HAART regimen. Physician should also discuss the side effects of prolong use of steroids with their patients which include cataract, elevated blood pressure, immunosuppression, avascular necrosis of hip, bone fractures and osteoporosis.

Conclusion

There are no evidence-based guidelines for the management of PML-IRIS. Future studies of the appropriate management of PML-IRIS will need to define the appropriate measures to ameliorate the effects of reactivation of JC virus without stimulating an excessively exuberant inflammatory response [11]. Our patient's clinical course suggests that a combination of steroids and HAART is useful. Well-controlled, prospective studies are warranted to identify the optimum time and dose of corticosteroids in conjunction with potent HAART for PML-IRIS.

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