Original Article

Study of clinical profile and outcomes in progressive multifocal leukoencephalopathy in acquired immunodeficiency syndrome patients in the highly active antiretroviral therapy era – An observational study

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Abstract

Background and Objectives: Progressive multifocal leukoencephalopathy (PML) is a viral infection affecting the central nervous system (CNS) seen mostly in advanced human immunodeficiency virus (HIV) infection. There is limited data on the epidemiology and disease course of these patients from India. This study was aimed to determine the frequency of PML in patients with HIV/acquired immunodeficiency syndrome (AIDS) and the clinical presentation and prognosis of these patients. **Materials and Methods:** The study was conducted at a tertiary care HIV center in New Delhi. Data of 765 patients from our anti-retroviral therapy (ART) clinic during a span of 4 years were retrospectively analyzed and reviewed. The diagnosis was based on the clinical and radiological picture and exclusion of other differential diagnosis by cerebrospinal fluid and serological studies. **Results:** Of 765 patients with HIV/AIDS, 12 (1.56%) were diagnosed with PML on the basis of consistent clinical and radiological features after ruling out other differential diagnosis. PML was the initial presentation of HIV infection in 8 (55.5%) patients. 11 (89%) patients had CD4 count <200/μl. Insidious onset focal limb weakness (50%) and dysarthria (50%) were common symptoms. Magnetic resonance imaging of the brain revealed characteristic white matter lesions in all the patients. The estimated median survival was 40 months (95% confidence interval, 23.88–53.19 months). **Interpretation and Conclusions:** Our results show that PML is associated with high morbidity despite the institution of highly active ART (HAART), but mortality has significantly declined if ART is started early. Key to good response is early diagnosis and HAART.

Key words: Acquired immunodeficiency syndrome, human immunodeficiency virus, JC virus, progressive multifocal leukoencephalopathy

Introduction

Progressive multifocal leuko-encephalopathy (PML) is an opportunistic infection of the central nervous system (CNS) caused by reactivation of JC polyomavirus (JCV) infection characterized by focal demyelination in the CNS.[1,2] It is almost always seen in the setting of profound immunodeficiency states, with acquired immunodeficiency syndrome (AIDS) being the most common predisposing condition responsible for approximately 80%–85% of all PML cases.[3] In the prehighly active antiretroviral therapy (HAART) era, the disease has been diagnosed in approximately 2%–5% of the human immunodeficiency virus (HIV) infected patients, as documented in data from developed countries mostly.[3,4] The incidence of PML has decreased but not as much when compared to other CNS diseases in the HAART era.[5] Interestingly, PML has been reported less commonly in HIV-infected patients from developing countries in general and India in particular.[6,7] We evaluated the epidemiological presentation of PML in patients with HIV/AIDS and the clinical features and

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prognosis of these patients at a tertiary care center in northern India.

Materials and Methods

The data of HIV/AIDS patients with PML seen at our center, a tertiary HIV care referral center over a 4 years period (Aug 2012 and Jul 2016) were retrospectively reviewed. The study included adult patients recruited from the ART clinic, various outpatient department, or inpatient facility of the hospital.

Data of all patients diagnosed with PML in the past 4 years were evaluated. Clinical diagnosis of PML is suspected when a patient presented with subacute onset of neurological deficits with previously known or freshly diagnosed HIV infection. All patients underwent a thorough clinical evaluation, including neurological assessment, cerebrospinal fluid (CSF) analysis, and magnetic resonance imaging (MRI) of the brain. The patients with PML are usually categorized as (i) Histology-confirmed PML (clinical and radiological features consistent with PML associated with histopathological diagnosis); (ii) laboratory-confirmed PML (compatible clinical and radiological features associated with the presence of JC virus DNA in cerebrospinal fluid); and (iii) possible PML (clinical and radiological findings consistent with PML with the exclusion of CNS lymphoma and opportunistic infections like tuberculosis, toxoplasmosis, cryptococcosis through CSF and serological analysis).[8,9] Most of the patients in India are diagnosed in the category of possible PML as JC virus DNA could not be done till recently due to nonavailability or prohibitive cost.

PML was also classified as Classic (PML in the setting of severe immunodeficiency) and Immune reconstitution inflammatory syndrome (IRIS)-related PML. PML-IRIS was defined as new onset or rapid worsening of PML shortly after initiation of HAART together with evidence of immune restoration (virological and immunological response demonstrated by a decrease in plasma HIV RNA level by more than 1 $\log_{10}$ copies/ml and an increase in CD4+ T cell count from baseline) and clinical symptoms and signs and MRI picture consistent with an infectious or inflammatory process involving the white matter. The symptoms could not be explained by a new infectious process or drug toxicity.[10] All patients were hospitalized for a detailed assessment initially. Investigations included hematological and biochemical parameters, CD4+ T-cell count, and plasma viral load. HIV infection was documented and further evaluated based on existing WHO and NACO guidelines.[11,12] Contrast-enhanced MRI imaging of the brain was performed in all the patients. Multifocal asymmetric white matter lesions, which were hyperintense on T2 and fluid-attenuated inversion recovery (FLAIR) sequences and hypo- to isointense on T1 were considered characteristic of PML. There was no mass effect or contrast enhancement and no restriction of diffusion. Lumbar puncture for CSF analysis was done for routine cytology and biochemistry. Polymerase chain reaction (PCR) for JCV detection was done in three cases. To rule out other disease processes CSF ADA, ZN stain, and MTB PCR for Tuberculosis, India ink stain, and Cryptococcal antigen testing for Cryptococcal meningitis, CSF Toxoplasma PCR if there was a strong suspicion of CNS Toxoplasmosis and VDRL to rule out neurosyphilis was done. In cases where a differential diagnosis of primary CNS lymphoma was considered, an MR Spectroscopy and PET-CT were also done.

On confirmation of diagnosis, these patients were started on HAART depending on existing ART guidelines as per NACO and WHO, which evolved from being Zidovudine based to Tenofovir during the study period. No separate treatment was given for PML except HAART. Patients were discharged and followed up on an OPD basis (except those who succumbed to the illness early) every month, 3 monthly or at least six monthly depending on patient availability and convenience. One patient presented with PML while on a failing second-line ART regime. He was started on integrase strand transfer inhibitor therapy in addition to existing backbone therapy. Patients who survived were followed up throughout the period and the remaining patients until death or loss to follow-up.

Statistical analysis

Continuous data are presented as mean ± standard deviation (for normally distributed variables) or median and interquartile range or IQR (for variable influenced by extreme values). Categorical data are presented as numbers with proportions. Survival distribution was estimated using the Kaplan–Meier method. All analysis was performed using SPSS (version 17; SPSS Inc., USA) SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.

Results

Of the 765 patients registered and followed up in the ART center during the study period, 72 patients presented with CNS manifestations, of which 12 (1.56% of total) patients were diagnosed with PML. Of these 12, nine (75%) patients were males. The mean age at diagnosis was 45.4 ± 7.8 years. CSF PCR for JC virus was tested in three patients and was negative in all. In 7 (58.3%) patients, PML was the first presentation of HIV infection. Four patients (33.3%) presented with PML while on antiretroviral drugs for more than 1 year as the first manifestation of treatment failure. One patient presented with PML IRIS. Important demographic, clinical, and laboratory characteristics of the patients are shown in Tables 1 and 2.

The mean CD4 count at the time of PML presentation was 90.6 cells/µl (Std dev 40.2). All except one, i.e., 11 (91.6%) patients had CD4 count lower than 200 cells/µl and one (8.4%) patient had count above 200 cells/µl at diagnosis of PML,

Table 1: Important demographic and laboratory characteristics of 12 patients with progressive multifocal leuko-encephalopathy

Patient characteristic	Data
Age (years)	45.4±9.05 (range 33-65)
Male: female	9:3
CD4 at diagnosiscells/cmm	90.6±40.2
CD4	
<100 (%)	8/12 (66.66)
100-200 (%)	3/12 (25)
>200 (%)	1/12 (8.33)
Plasma VL at diagnosis (copies/ml)	$7.66\times10^5\pm5.36\times10^4$
PVL>10^5 (copies/ml) (%)	5/9 (55.55)
10^5-10^3 (copies/ml) (%)	3/9 (33.33)
<10^3 (copies/ml) (%)	1/9 (11.12)
Diagnosis as the first presentation of HIV infection (%)	7/12 (58.3)
Diagnosis as presentation of treatment failure (%)	4/12 (33.3)
Presentation as IRIS (%)	1/12 (8.33)

IRIS=Immune reconstitution inflammatory syndrome; HIV=Human immunodeficiency virus

Table 2: Common clinical presentations

Clinical features at presentation	Numbers (%)
Focal limb weakness	6/12 (50)
Speech disturbance	6/12 (50)
Visual disturbance	3/12 (25)
Cognitive dysfunction	5/12 (41.6)
Seizure	2/12 (16.66)
Ataxia	5/12 (41.6)
Pure cerebellar syndrome	2/12 (16.66)

eight (66.6%) patients had CD4 <100 at presentation. Viral load was tested in nine (75%) patients of whom five (55%) had viral load above 100,000 copies/ml, three (33.3%) had viral load between 1000 and 100,000 and one (11.1%) patient had viral load <1000 copies/ml. Clinical features at presentation were variable. Motor deficits with focal limb weakness or spasticity were seen in 6 patients (50%). Cognitive and behavioral disturbance was seen in five patients (41.6%), visual abnormality in three (25%), cerebellar signs, including gait ataxia in five (41.6%), of which two patients had pure bilateral cerebellar dysfunction at presentation. Only two patients had seizures at the time of diagnosis. CSF analysis was available for all 12 patients and showed mildly elevated protein in six patients (>45 <100 mg/dl), pleocytosis in three patients (all mononuclear cells, max cell count 30/mm^3) with normal CSF glucose level in all of them. CSF analysis for JC virus detection was performed in three patients and found to be negative in all three. CSF ADA levels were within the normal limits, CSF Mtb PCR, Cryptococcal antigen, VDRL were negative. Gram, India ink, and ZN stain were also negative in all cases. Multifocal white matter lesions in cerebral hemispheres were seen in MRI of all patients. These lesions appeared hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images [Figures 1 and 2], and were not associated with contrast enhancement in all except PML IRIS). Eleven (91.66%) patients presented with classic PML and IRIS-related PML were diagnosed in one (8.33%) patient on the basis of new-onset symptoms 3 months after starting ART with the documented rise in CD4 and more than one log decline in Viral load.

During the study period, two (16.66%) patients died, one (8.33%) was lost to follow-up, and nine (75%) continued to follow-up. Among the two patients who died, one died within 2 months of diagnosis directly due to the effects of worsening neurological condition, and the other patient succumbed to carcinoma Anal canal 18 months after the diagnosis of AIDS and PML. All other nine patients have shown neurological improvement and stabilization and are on regular follow-up of which two (16.66%) patients are on follow up for more than 5 years, three (25%) patients between 3 and 5 years, one (8.33%) patient between 1 and 3 years and three (25%) patients are on follow up for <1 year.

The Kaplan–Meier curve depicting the cumulative probability of survival is shown in [Figure 3]. The median survival was 40 months (95% CI 23.88–56.11 months).

Discussion

The incidence of PML in HIV in considered to be low in India compared to Western countries. In the present study, 1.56% of the patients attending the ART clinic had PML. It is less common compared to developed countries, where it has been reported in up to 5% of patients.[8] Review of literature from India revealed two significant studies, namely Sharma *et al*. and Shah *et al*., in which reported incidence varied from 1.2% to 3.5%, respectively.[7,13]

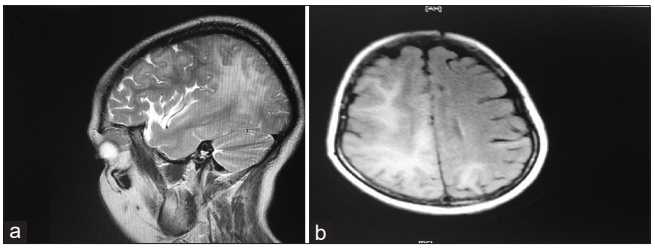

Figure 1: A 47-year-old woman presented with subacute onset progressive weakness of the left upper limb followed by lower limb with visual impairment in the left eye and dysarthria over a period of 4 weeks duration. Magnetic resonance imaging brain shows diffuse bilateral asymmetrical altered signal intensity lesions in the subcortical (arcuate U-fibers) and deep white matter in the right Fronto -parieto- temporal region and left occipital lobe, midbrain superior colliculus, and cerebral peduncles. Lesions were hyperintense on T2 and fluid-attenuated inversion recovery and hypointense on T1 with no mass effect or contrast enhancement.(a) MRI Brain Saggital section T2 weighted image (b) MRI Brain Axial section T2 weighted image

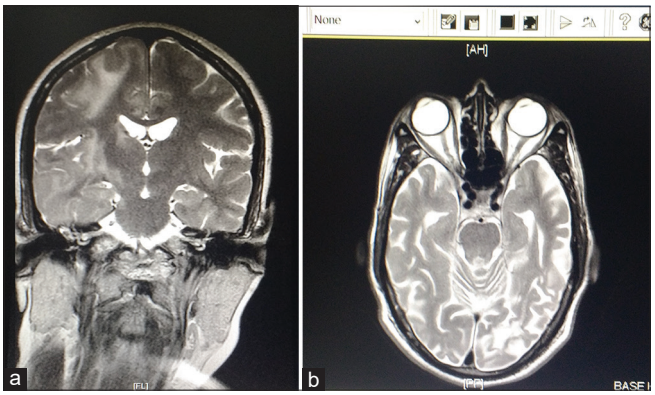

Figure 2: A 48-year-old man presented with subacute progressive cognitive decline and loss of vision. Magnetic resonance imaging revealed asymmetric T2 and fluid-attenuated inversion recovery hyperintensities in deep periventricular white matter in bilateral parietal and left occipital lobes with no mass effect, no contrast enhancement, and no true restriction on diffusion-weighted imaging .(a) MRI Brain Coronal section T2 Weighted image (b) MRI Brain Axial section T2 weighted image

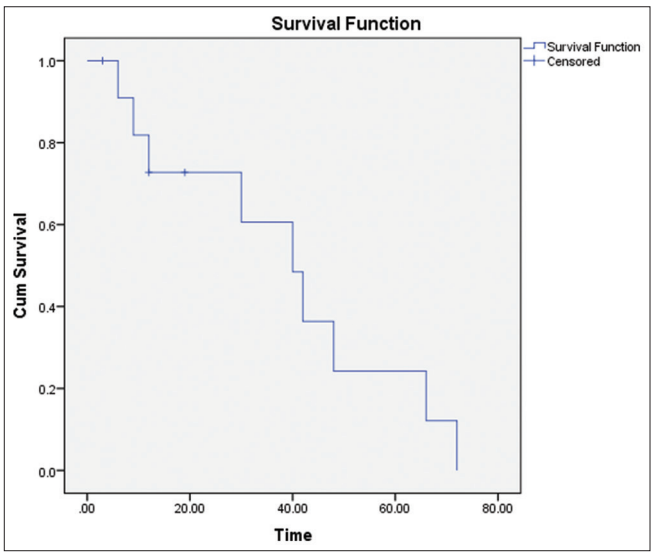

Figure 3: Survival probability of patients with progressive multifocal leukoencephalopathy estimated using the Kaplan–Meier method

In this study, majority of patients had advanced immunosuppression at the time of diagnosis of PML with CD4 <200 cells/µl. However, it has also been reported in patients with CD4 counts in excess of 200 cells/µl

occasionally[14,15] as seen in one of our patients. In seven of our 12 patients (58.3%), PML was the first presentation of HIV infection and in four cases the first presentation of treatment failure leading to AIDS. Focal weakness in one of the extremities, cognitive impairment, and dysarthria were the common manifestations.[14,16,17] PML-IRIS was diagnosed in one (8.33%) of our patients in the study and the radiological picture, in this case, was different from other cases in having mild contrast enhancement of the lesions. The median survival was 40 months, which is significantly higher than that seen in most previous studies published in India or western countries in the HAART era.[14,15] Only one of our patients died due to progressive neurological deterioration after starting HAART and one patient succumbed to an AIDS-related malignancy 18 months after starting HAART. The 1 year survival rate in our patients was >90%. It probably represents the changing trends and improving outcomes in PML patients with early diagnosis and institution of HAART. In the pre-HAART era, the prognosis of PML was dismal, with a median survival of 2.5–4 months[18,19] with most deaths occurring in the first few months. Various treatment strategies directed against JC virus have been unsuccessful and HAART remains the only proven effective therapy.[20] Other studies have also shown that survival has increased substantially after the introduction of HAART with reported 1-year survival of 39%–56%.[21-23]

Limited access to diagnostic facilities is a major roadblock to the diagnosis of PML and results in underdiagnosis or underreporting from resource-constrained settings such as India. The limitation of our study arises from the resource constraints, which precluded histological proof of diagnosis. JC virus detection in CSF could be done only in a limited number of cases due to the prohibitory cost of these tests. Most of the cases were in the category of possible PML. However, CSF analysis and relevant investigations were done to rule out other differential diagnosis. Most cases showed partial regression of lesions in consonance with clinical stabilization. MRI repeated in some cases after a few years showed postinflammatory and gliotic white matter changes indistinguishable from other long-standing white matter inflammatory disorders.

Conclusion

To conclude, PML in HIV patients in India is relatively less common but not as less as previously thought considering that a large number of patients may be undiagnosed or unreported due to lack of definitive diagnosis. The overall survival has shown remarkable improvement (median survival 40 months) from the past reports likely due to early diagnosis and early aggressive institution of HAART. However, patients not responding to HAART showed rapid neurologic deterioration leading to death. All patients had classical MRI pictures. The incidence of IRIS-PML was low. The incidence of PML is likely to be further reduced in India with the implementation of the latest ART guidelines recommending ART for all patients at diagnosis irrespective of CD4 counts.

We need more studies from India to generate epidemiological data like the JC virus positivity rate in CSF of PML patients in India to improve diagnostic capability and early management of these patients along with providing wider and early access to HAART to improve outcomes. Finally, there is also a need to research for newer therapeutic options directly targeted against the JC virus.

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Conflicts of interest

There are no conflicts of interest.

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