Clinical Profile and Outcome of Progressive Multifocal Leukoencephalopathy in HIV Infected Indian Patients

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Abstract

Background and objectives: Progressive multifocal leuкоencephalopathy (PML) is a fatal demyelinating disease of the Central nervous system (CNS) caused by the human polyoma virus JC (JCV). Human Immunodeficiency Virus (HIV) infection predisposes to PML. Very sparse data is available regarding the effect of Highly Active Anti Retroviral Therapy (HAART) on clinical outcome of PML in Indian settings. This study was carried out to look into clinical profile, survival and neurological outcome of HIV infected PML patients in HAART era.

Methods: We looked in our cohort of HIV-1–infected individuals retrospectively. Diagnosis of PML was done on basis of clinical and radiological abnormalities highly suggestive of the condition, with or without confirmation of JCV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR).

Results: Out of 892 HIV infected patients, 31 met the criteria for the diagnosis of PML. The median CD4⁺ cell count was 73 cells/μL (Interquartile range (IQR), 43-160 cells/μL) at the presentation of PML. Median duration of PML symptoms were 30 days (IQR, 15-60 days) before diagnosis of PML could be made. The median survival was 538 days. In those patients who survived more than one year, the median survival time was 1095 days (95% confidence interval (CI), 1090.35 – 1099.64 days). Those who survived more than one year (n=13), Neurologic function were categorized as cure or improvement in 8, same status in 3 or progression in 2 patients.

Conclusion: In the pre-HAART era, PML patients had very poor prognosis with median survival of 4-6 months after diagnosis. Till date HAART is the only way for reversal of immune system in HIV infected patients and its prompt institution is the most effective therapeutic approach in increasing survival in this group. In this study, 46.4% patients survived after 1 year on HAART. Amongst them, 69% patients completed 3 years. There is strong need of research for the development of pharmacotherapy against JC virus to increase the survival.

Editorial Viewpoint

• PML is a fatal demyelinating disease in HIV infected patients.
• In the era of HAART survival in PML patients has improved.

Introduction

Progressive multifocal leuкоencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the human polyomavirus JC (JCV).¹

The number of PML cases has increased rapidly with the spread of human immunodeficiency virus type I (HIV-1) infection.² PML was an AIDS defining condition usually occurs in advanced disease with CD4⁺ cell count <100/μL.³ PML occurs in 1 to 10% of AIDS cases.⁴ Fifty five to eighty five percent of all PML cases are seen in HIV infected individuals.⁵ Clinically, PML was characterized by progressive neurologic deficits leading almost invariably to death with a median survival of few months after diagnosis in pre HAART era.⁶ Complaints of limb weakness, gait disturbances and speech disorders are the most common symptoms reported by patients with PML.⁷,⁸ Radiologically, the brain lesion in PML is classically a white matter lesion, hypointense in T1 weighted images and hyperintense on T2 weighted images, without contrast enhancement and mass lesion. In most cases, PML is fatal, usually within few months from onset. Since there is no specific therapy, reversion of the immune suppression, when feasible, remains the only proven approach for management of this disease.

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Material and Methods

In this retrospective study we looked into the cohort of HIV-1 infected patients across the globe. However, solid data about the effect of HAART on the outcome of AIDS-associated PML is lacking from India. The objectives of our study were to analyze clinical profile, patient survival, the neurologic function of patients of PML in a cohort of patients treated with HAART.

There are very few studies which looked into the outcome of PML in HIV infected patients across the globe. However, solid data about the effect of HAART on the outcome of AIDS-associated PML is lacking from India. The objectives of our study were to analyze clinical profile, patient survival, the neurologic function of patients of PML in a cohort of patients treated with HAART.

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### Table 1: Presenting symptoms in patients with PML (N=31)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb paresis</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Difficulty in speech</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Difficulty in walking</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>Cognitive defects</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

During the study period that is from 1st June 2007 to 31st May 2011, out of 892 HIV positive individuals, 31 patients met the criteria for the diagnosis of PML. Over all incidence was 3.5%. The median age of patient was 40 years (Interquartile range (IQR): 35-47 years); 64.5% (n=20) of the patients were male. In 77% (n=24) of patients, CD4 count at the time of diagnosis of PML was less than 200 cells/µL. The median CD4+ cell count was 73 cells/µL (IQR, 43-160cells/µL) at presentation of PML. Those who had PML as index diagnosis had median CD4 cell count of 68/µL while those who developed PML later on had median CD4 cell count 153/µL (Figure 1). Almost one third (64.5%, n=20) patients had acquired HIV infection through heterosexual route, while 19.4% (n=6) had transmission through blood. In 5 (16.1%), the mode of HIV transmission was unknown.

In 55% (n=17) of patients PML was the index diagnosis (Presenting manifestation). Median days of duration of PML symptoms were 30 days (IQR, 15-60 days) before diagnosis of PML. The predominant neurological symptoms of PML at presentation were limb paresis (39%, n=12), speech disturbances (39%, n=12), coordination disturbance (29%, n=9), cognitive defects (23%, n=7), visual disturbance (10%, n=3) and seizure (10%, n=3) as shown in Table 1. Most common signs were limb weakness (48%, n=15), alterations of speech (39%, n=12) and lack of coordination, (45%, n=14) as shown in Table 2. On MRI examination, Supratentorial lesions were found in nearly 90% (n=28) of the patients, and infratentorial lesions were found in 52% (n=16).

After diagnosis of PML, all except two patients received antiretroviral therapy (ART). Out of 29 patients on ART, 24 (82.8%) patients were on non-nucleoside reverse transcriptase inhibitor (NNRTI) based therapy while 5 (17.2%) were on protease inhibitor
(PI) based therapy as per national guidelines.

Three patients were lost to follow up. Total 15 patients died within 1 year after diagnosis of PML. Seventeen (60.7%), fifteen (53.6%) and thirteen patients (46.4%) remained alive after 3 months, 6 months and 1 year respectively. Those who survived till one year, all remained alive till censored date, 9 patients completed three years and another 3 completed two years. For those 28 patients who remained on follow up, the median survival was 538 days (95% confidence interval (CI), 1090.35 –1099.64 days). The results of univariate analysis of variables associated with mortality in patients with PML are shown in Table 3. None of the variables affected survival. Neurologic function in survivors was categorized as cure or improvement in 8, same status in 3 or progression in 2 patients.

In our cohort, 5 patients developed symptoms of PML after initiation of ART. Three patients were considered as Immune reconstitution inflammatory syndrome (IRIS) as they presented within 3 months of starting ART. Two out of these three patients shown contrast enhancing lesions in MRI. Out of these three patients, 2 survived and both had stable neurologic functions. Two patients who developed PML lesions on MRI after two years of starting ART, however plasma viral load was undetectable in both. Both patients survived, however one improved on same ART while other patient had shown progressive neurological dysfunction.

**Discussion**

Fifty three point six (53.6%) percent of patients with PML died despite receiving antiretroviral therapy in our study. All these patients died within one year and majority of them within 6 months. Those who remained alive after one year are all surviving till the end of study.

The most common predisposing cause for PML is Acquired immunodeficiency syndrome (AIDS) in comparison to other immunosuppressive conditions like malignancy, transplantation, autoimmune disorders, etc.9 The incidence of PML in HIV infected patient from developed countries has declined after the introduction of HAART.3,7,10 Most of the PML patients from India have been reported as case reports or case series. Recently two studies, one from North India11 and another from South India,12 reported PML as 1.2% and 2.8% respectively in their HIV cohort. In our cohort 3.5% of HIV patients developed PML. It is comparable to developed countries, where it has been reported in up to 5% of patients.9

In our study, more than half (55%) of patients had PML as index diagnosis or presenting manifestation of HIV. Similar results have been documented in study from India11 and western countries.9 In remaining 45% of patients, 16% has developed PML after starting HAART and rest
(29%) of had some other presenting disease as index diagnosis. Majority of patients had advance HIV/AIDS with CD4 count less than 200/µL (median CD4+ cell count-73 cells/µL) at the time of diagnosis of PML. Those patients who presented with PML as index diagnosis had significantly low CD4 count as compared to the remaining patients (mean CD4 count 68 v/s 153; p <0.000). Similar to other study,7 in our cohort, PML occurred in patients who presented late or as result of failure of HAART. This shows that PML as disease of advanced immunosuppression.

There are no significant differences between clinical, radiological, and pathological picture of PML between India and Western countries.12 In this study also, presenting symptoms in descending order were limb paresis, speech disturbances, coordination disturbance, cognitive defects, visual disturbance, seizure and headache. Gait abnormality, limb weakness, alterations of speech and lack of coordination were common examination findings while cranial nerve involvement and involuntary movement were found in very small number of patients. Exclusive infratentorial PML lesions were found only in 10 percent of patients while majority of patients had either supratentorial alone or both region lesions on MRI findings. Similar findings were found in European studies.7,8

In the pre-HAART era, PML patients had very poor prognosis. Most of them had fatal course and died in a median period of 4-6 months after diagnosis.1,13,14 There is no specific antiviral therapy for JC virus causing PML. The only way to improve prognosis is reversal of immunosuppression.15 The HAART is the only way for reversal of immune system in HIV infected patients and the prompt institution of it is the most effective therapeutic approach in increasing survival in this group.16 Probability of survival at one year was documented to be 50% on HAART as compared to 5% in patients not receiving HAART.17,18 Similarly significant reduction in PML-attributable one year mortality has been documented in Swiss HIV Cohort Study.3 Subsequently in one large study of 118 consecutive PML patients with HIV infection, (63.6%) remained alive for a median of 114 weeks (2.2 years) after diagnosis of PML.9 Long-term survival is now observed.10 In our study, 46.4% patients remained alive after 1 year. Amongst them, 69% patients completed 3 year till censored date. The median survival was 538 days for patients except loss to follow up. In those patients who survived more than one year, the median survival time was 1095 days (95% confidence intervals (CI), 1090.35–1099.64 days) which was higher than that documented from North India.11 Antiretroviral therapy that especially included protease inhibitor (PI) was once shown to be reducing risk of death significantly in PML patients.15 Subsequently no advantage of PI based treatment over NNRTI based regimen has been found.19 In our study all patients got NNRTI based regimen except those who developed PML on failing first line ART.

We were not able to identify any baseline variable with prognostic significance like age, gender, duration of PML symptoms before starting HAART, PML as index diagnosis, CD4 cell count <100/µL or site of PML lesion in Brain. A western study has shown similar result except CD4 cell count < 100/µL as risk factor of prognostic significance for mortality.8 However, subsequently in another study19 CD4 cell count <100 or <200/µL were not associated with mortality.

Earlier study had shown either no clinical improvement or marginal improvement that to in fewer number of patients who received HAART.20 Later on, in GESIDA 11/99 Study Group, there was improvement in neurologic status in almost 50% of survivors.6 In Recent study, there was marked improvement or stabilization of neurologic deficit (in 66 to 83%) in survivors of more than 3 years.7,16 In our study, 84% of the survivors after one year have shown either improvement or stabilization.

In our cohort, 16% (n=5) of patients developed PML after successful HAART. Three out of five patients presented within 3 months were considered as true IRIS. Amongst these, two patients had shown contrast enhancement of lesions on MRI findings. For the remaining 2 patients, we may call them late IRIS as both had undetectable virus in blood and developed PML lesion after 2 years of starting HAART. Delay in restoration of immune function may be the explanation as suggested in previous study.12 Rate of PML IRIS found to be the lowest in Swiss HIV Cohort Study (2.5%)3 while highest rate found to be 23%.17 Eighty percent of our PML IRIS patients survived as against all patients in western study.19

However, this retrospective study has some limitations. Majority of patients are diagnosed as PML by clinical and typical radiological findings. None of the patient was subjected for any histological evidence and only limited patients had been evaluated for JC virus PCR in CSF. However, there was no difference found in the prognosis of patients in both groups whether confirmed diagnosis or probable diagnosis of PML.7

In conclusion, HAART has changed the prognosis of PML with 46.4% survival at one year (median survival 1095 days), in compare to fewer months (median survival 4 to 6 months) in pre HAART era. However still there is strong need of research for the development of pharmacotherapy against JC virus to increase the survival and quality of life.

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References