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Commentary

Progressive multifocal leukoencephalopathy, a rare but devastating disease in AIDS patients

Epidemiological studies estimate that the current median survival is more than 35 years for a young person diagnosed with HIV infection in the highly active antiretroviral therapy (HAART) era if the patient is appropriately diagnosed and treated[1]. Unfortunately, a significant number of patients are still diagnosed at advanced stages of HIV infection which worsens the prognosis. This is the case of patients who are diagnosed with progressive multifocal leukoencephalopathy (PML). Before the advent of HAART, PML was reported to be developed in 3-7 per cent of HIV-1-infected patients and comprised up to 18 per cent of fatal CNS diseases[2]. This frequency has decreased substantially in the current treatment era, though not to the same extent as other opportunistic infections. Although PML can be considered a rare disease, it continues to occur, and now it has probably become the deadliest opportunistic infection in patients with AIDS. In this issue there is an excellent clinical description of a series of cases of PML diagnosed at a tertiary care centre in New Delhi, India[3]. The authors present a retrospective study of 18 patients diagnosed with PML between 2006 and 2011. There are some aspects in this study that deserve some comments.

Most cases were classified as possible cases because they were diagnosed in patients with clinical and radiological findings consistent with PML after exclusion of other diseases that can affect the central nervous system (CNS) but without laboratory confirmation. In fact, only four (22%) patients in this study had a laboratory confirmed diagnosis. Although this percentage of confirmed diagnosis is low, yet it is not very different to what has been reported in other studies[4]. A definitive diagnosis of PML requires the detection of JC virus (JCV) in cerebrospinal fluid (CSF) by PCR testing. JCV detection by PCR has a sensitivity that ranges from 72 to 92 per cent and a specificity from 92 to 100 per cent according to studies performed before the HAART era[5]. However, in recent years, it has been common to find patients with clinical and neuroradiological findings consistent with PML but with negative JCV PCR detection in CSF. Among 101 cases with PML in the Italian Registry NeuroAIDS study in 2000-2002, only in 49 of 84 (58.3%) patients, JCV was detected by PCR in CSF samples[6]. This percentage of detection is lower than the sensitivity of JCV PCR reported in the pre-HAART era. The low detection rate in these studies may be partly due to lack of sensitivity of the technique. Other study reported that the sensitivity of JCV PCR dropped from 89.5 per cent in the pre-HAART era to 57.5 per cent in the HAART era, perhaps due to HAART re-establishing host immune function and reducing JCV below detectable levels[7]. All these figures indicate that diagnosis of PML is an area that needs improvement.

Some clinical aspects of PML have evolved from the initial PML cases diagnosed in the pre-HAART era. PML was classically associated with severe immunosuppression, and most patients had a very low number of CD4 lymphocytes[8,9]. Unlike most of the other HIV-associated CNS opportunistic infections, which are very rare when the CD4-cell count is higher than 100-200 cells per µl, PML occasionally occurs in patients with much higher CD4-cell counts. In the present study, two of the 18 patients had a CD4 cell count above 200 cells/µl. These data were also observed in the Italian Registry Investigative NeuroAIDS in 101 cases notified between 2000 and 2002. In this study 16.8 per cent of patients had more than 200 CD4 lymphocytes when PML was diagnosed[6]. A possible explanation for this phenomenon is the diagnosis of PML as a manifestation of the immune reconstitution inflammatory syndrome (IRIS). Patients who have new onset or worsening of PML shortly after initiation of HAART have been well described. This clinical

presentation occurs in the setting of a recovery of the immune system characterized by an increase in the CD4 lymphocyte count and a sharp decrease in HIV-1 viral load. In the study presented in this issue[3], four (22%) patients had an IRIS related PML, in three of them symptoms of PML developed after initiation of HAART and the remaining presented a paradoxical IRIS. This percentage of cases of PML-associated IRIS is similar to what we have observed in our setting where IRIS was diagnosed in 23 per cent of the patients[4].

The most important aspect to consider is the poor prognosis of patients diagnosed with PML. Data presented in this issue show that 61 per cent of the patients died and only 28 per cent continued to follow up[3]. The median survival time was 7.6 months. Before the introduction of HAART, the median survival time for PML was 8-15 wk[10]. Although some progress has been made after the widespread use of HAART, data from European cohorts are still worrying. In a nationwide population-based cohort study of adult HIV-1 infected individuals in Denmark, 47 patients with PML were identified between 1995 and 2006. Although the median survival time improved from 0.4 years in 1995-1996 to 1.8 years in 1997-1999 and 2000-2006, the overall mortality remained extremely high since 35 of the 47 patients died[11]. In another multicenter study performed in Barcelona, Spain, between 2002 and 2006 the mean survival time of patients with PML treated with HAART was 16 months and the estimates of the probability of survival at 36 months was only 27.6 per cent[4]. A recently published study identified 24 PML patients who survived more than five years from the disease onset[12]. All of them were treated with HAART. This study shows that some patients with PML may achieve an extended survival and, although none recovered entirely, one third of them were left with no significant functional disability.

The mainstay of treatment for PML in patients infected with HIV is immune reconstitution with HAART. None of the proposed treatments for PML, including cytarabine, alpha-interferon, and cidofovir, has had any influence on disease progression. Cellular responses mediated by CD4 and CD8 lymphocytes play a key role in JCV disease control, and restoring the immune response to JCV by HAART seems to be an important clue to improve PML prognosis. Recently a multicenter, open-label pilot trial evaluating the survival benefit of a five-drug antiretroviral regimen designed to accelerate HIV replication decay and JCV-specific immune recovery has been published[13]. In this study, 28 patients diagnosed with PML received an optimized HAART regimen with three or more drugs for 12 months, plus the fusion inhibitor enfuvirtide during the first six months. Seven patients died, all before month 4 and the one-year survival estimate was 0.75 (95% confidence interval, 0.61 to 0.93). At month 6, JCV DNA was undetectable in the CSF of 81 per cent of survivors. The authors concluded that the early use of five antiretroviral drugs after PML diagnosis appeared to improve survival. This was associated with the recovery of anti-JCV T-cell responses and JCV clearance from CSF. Though these results need to be confirmed in future studies, these open a promising line in the treatment of these patients.

Currently we have no effective treatment for PML apart from HAART. The prompt institution of HAART in HIV infected PML patients is the most effective therapeutic approach. It is certain that with HAART the incidence of this infection has slightly decreased and the survival has improved. However, for patients who develop PML the prognosis continues to remain uncertain. Strategies to improve early diagnosis and treatment of HIV infection are nowadays the only way to avoid the emergence of new cases of PML.

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