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Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy

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Abstract

Progressive Multifocal Leukoencephalopathy (PML) is a demyelinating disease of the brain caused by the polyomavirus JC (JCV) in immunosuppressed people. There is no cure for PML but one-year survival has increased from 10% to 50% in HIV-infected individuals treated with highly active antiretroviral therapy (HAART). We describe herein the clinical outcome of 24 PML patients whose survival exceeded 5 years, with a mean follow-up of 94.2 months (range 60–188 months). Of all patients, only 2 were females including one who had non-Hodgkin's lymphoma and was HIV-negative. All 23 HIV-positive patients received HAART, and additional experimental therapies were not associated with a better clinical outcome.

Marked neurological improvement occurred in 4/24(17%) of patients, while 11/24 (46%) had partial improvement and 9/24(37%) remained stable. By the end of the period of observation, 8/24(33%) of patients had no significant disability despite persistent symptoms (modified Rankin disability scale (MRDS) =1), 6/24(25%) had slight disability and were living independently (MRDS=2), 5/24(21%) were moderately disabled, requiring some help during activities of daily living (MRDS=3) and 5/24(21%) had moderately severe disability, requiring constant help or institutionalization (MRDS=4). Patients with cerebellar lesions tended to have a worse clinical outcome.

MRI showed leukomalacia with ventricular enlargement secondary to destruction of the white matter at the site of previous PML lesions, and focal areas of subcortical atrophy with preservation of the cortical ribbon.

Of 20 patients tested, 19(95%) had detectable CD8+ cytotoxic T-lymphocytes against JCV in their blood. In absence of a specific treatment, immunotherapies aiming at boosting the cellular immune response against JCV may improve the prognosis of PML.

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Introduction

Progressive Multifocal Leukoencephalopathy (PML) is a rare demyelinating disease of the CNS caused by reactivation of JC virus (JCV)1. Primary infection occurs in childhood and the virus remains latent in the kidney or lymphoid organs thereafter. In the setting of cellular immunosuppression, the virus may spread to the central nervous system, leading to a lytic infection of oligodendrocytes and subsequent demyelination. Classically, PML was observed in patients with advanced HIV infection, lymphoproliferative disorders and transplant recipients. Hovewer, the use of new selective immunomodulatory or immunossupressive medications —such as natalizumab, efalizumab and rituximab—has recently altered the epidemiology of PML, which has now also been diagnosed in patients with psoriasis, rheumatoid arthritis, multiple sclerosis or Crohn's disease2.

There is no specific treatment for PML, but the survival in HIV-infected PML patients has increased substantially during the last decade. Before the introduction of highly active antiretroviral therapy (HAART), only 10% patients with PML lived for more than a year and patients usually survived only weeks to months after the diagnosis was made3. In contrast, recent studies have shown at least 50% one-year survival of HIV- infected PML patients4 5. However, the prognosis of PML associated with other immunosuppressive conditions remains poor.

Since until recently, long-term PML survivors were extremely rare, the clinical outcome of this group of patients has not been characterized in detail. Herein, we describe the clinical features and disability profile of PML patients whose survival has exceeded five years.

Methods

We reviewed the records of PML patients followed in clinical studies at the HIV/Neurology Center of the Beth Israel Deaconess Medical Center, the Massachusetts General Hospital and the Washington University School of Medicine between January 1992 and December 2006. We included a total of 24 patients with diagnosis of PML confirmed by biopsy (n=2) or the detection of JCV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) (n=16). We also included patients with clinical and radiological features and evolution typical of PML but negative JCV CSF PCR, based on consensus terminology criteria (n=6) 6. These patients had a negative work-up for other CNS infections or tumors. Long-term survivors were defined as survival exceeding 5 years (sixty months) from onset of PML symptoms by 12/31/06. The degree of disability was measured using the Modified Rankin disability scale (MRDS)7. The cellular immune response against JCV was measured using ^{51}Cr release or tetramer staining assays as previously described 8.

Results

We identified 24 PML patients who survived more than 5 years from disease onset. Among them, 22 (92%) were men and 2 (8%) women. The mean age at onset of PML was 38 years (range 31–54 years). The predisposing condition in all patients was HIV infection, except one who had non-Hodgkin's lymphoma (Patient #6, table 1). The mean length of follow up was 94.2 months (range 60–188 months).

Clinical features at diagnosis and treatment are described in Table 1. All HIV-infected individuals received HAART. Two patients received cytosine arabinoside (ARA-C). Four patients were treated with α interferon (IFN- α), while two patients were treated with the 5HT2a serotonin receptor antagonist mirtazapine. Marked improvement of neurological function was observed in 4/24 (17%) of patients, while 11/24 (46%) had partial improvement and 9/24 (37%) remained stable. At the end of the period of observation, 8/24

(33%) of patients had no significant disability despite persistent symptoms (MRDS =1), 6/24 (25%) had slight disability and were living independently (MRDS=2), 5/24 (21%) were moderately disabled, requiring some help during activities of daily living (MRDS=3) and 5/24 (21%) had moderately severe disability, requiring constant help or institutionalization (MRDS=4). There was a trend towards a worse long-term disability (MRDS 3 and 4) in patients who presented with cerebellar features (5/7; 71%) when compared with patients who developed other neurological syndromes (5/17; 29%) (p= 0.08).

None of the patients enjoyed a complete recovery. Conversely, no patient became bedridden. However, 5/24 (21%) developed seizures, including generalized tonic-clonic in three patients and focal motor seizures in two, which were successfully treated with levetiracetam monotherapy or in combination with gabapentin or topiramate.

Late radiological aspects of PML lesions in long-term survivors included leukomalacia with subsequent ventricular enlargement secondary to destruction of the white matter, as well as focal areas of subcortical atrophy. Despite extensive damage in the affected areas, there was preservation of the cortical ribbon. Three representative cases are shown in Figure 1.

The median CD4 count of the 23 HIV+ PML patients at the end of the period of observation was 389/μl (range 127–984) and 19/23 (83%) had undetectable HIV RNA in the plasma. Finally, we measured the cellular immune response against JCV in 20 subjects, and JCV-specific CD8+ cytotoxic T-lymphocytes (CTL) were detectable in the blood in 19 of them (95%).

Discussion

PML is an evolving disease and important changes in epidemiology have been observed recently. Indeed, immune recovery associated with HAART has resulted in a better prognosis for HIV-infected PML patients. In fact, PML is becoming a chronic disease—rather than a fatal disease—in a growing number of HIV-infected patients. For this reason, it is important to understand the clinical outcome of long-term survivors of PML in HIV-infected patients. In contrast, HIV-negative patients who develop PML in the setting of hematologic malignancies, treatment for auto-immune diseases or organ transplantation, more rarely achieve a meaningful restoration of their immune system supporting survival. While such patients account for 20% of PML cases9, only 1/24 (4%) of long term-survivors in our cohort had a predisposing disease other than HIV. Interestingly, the overwhelming majority of tested subjects had a detectable cellular immune response against JCV, which confirms previous studies on the role of T lymphocytes in PML survival8 10.

Our 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 prompt institution of HAART in HIV infected PML patients is the most effective therapeutic approach in increasing survival in this group. Several studies have shown that PML survival increased from 10 to 50% in the last decade4 11. However, data on long-term neurological sequelae in PML survivors is still scarce. In our study, we observed that 66.6% of survivors improved or were stable in their deficits after five years from onset of symptoms. This finding is in accordance with a recent Danish study that reported improvement or stabilization in 83% of patients after three years of follow-up12. Another study reported improvement in 33 of 75 patients (44%)13. In our study, severe neurologic impairment was observed in almost one third of survivors. A similar picture was described in a recent study where 39% of PML patients surviving 12 months had a MRSD ≥ 4 5.

These data indicate that in some cases, PML may indeed become inactive or “burnt out”, leaving patients with permanent neurological deficits reflecting the functional brain region

lesioned by the infection. Interestingly, lesions affecting the cerebellum tended to be more disabling, associated with gait ataxia and incoordination, precluding independent living.

Over the years, several drugs such as cidofovir 5, topotecan14, and interferon α(IFN- α)15 have been investigated for the treatment of PML, with disappointing results. A retrospective analysis showed stabilization of PML in one-third of HIV-negative patients with leukemia or lymphoma who developed PML after intravenous administration of cytarabine (ara-C), but hematological toxicity remains a limiting factor with this drug16. A randomized controlled trial in HIV-infected patients with PML failed to show any benefit of cytarabine. Recently, it has been shown that JC virus entry in astroglial cells *in vitro* is mediated in part through the 5HTA2 receptors17. Mirtazapine, an antidepressive drug which blocks the 5HTA2 receptor has been used empirically in an attempt to limit virus spread within the brain and delay progression of disease. However, except for HAART, none of the medications taken by the patients in the present study appeared to be associated with a better clinical outcome, although there is limited power to detect an effect because of the small sample size. In absence of a specific treatment for JCV, immunotherapies aimed at boosting the cellular immune response against this virus may well improve the prognosis of PML. In a recent study, JCV-peptide loaded dendritic cells from PML patients, HIV-infected individuals and healthy control subjects could elicit a strong cellular immune response mediated by CD8+ cytotoxic T lymphocytes cell response *in vitro*18, which suggests that autologous dendritic cell-based immunotherapy could be a potential therapeutic option for PML.

Since a cure for PML is currently not available, re-establishing latency of this infection is critical to survival. Our observations suggest that this is now possible, allowing modest functional recovery. Remarkably, the immune reconstitution achieving latency has been persistent, and none of the patients described in our study experienced another clinical reactivation of JC virus after their first episode of PML.

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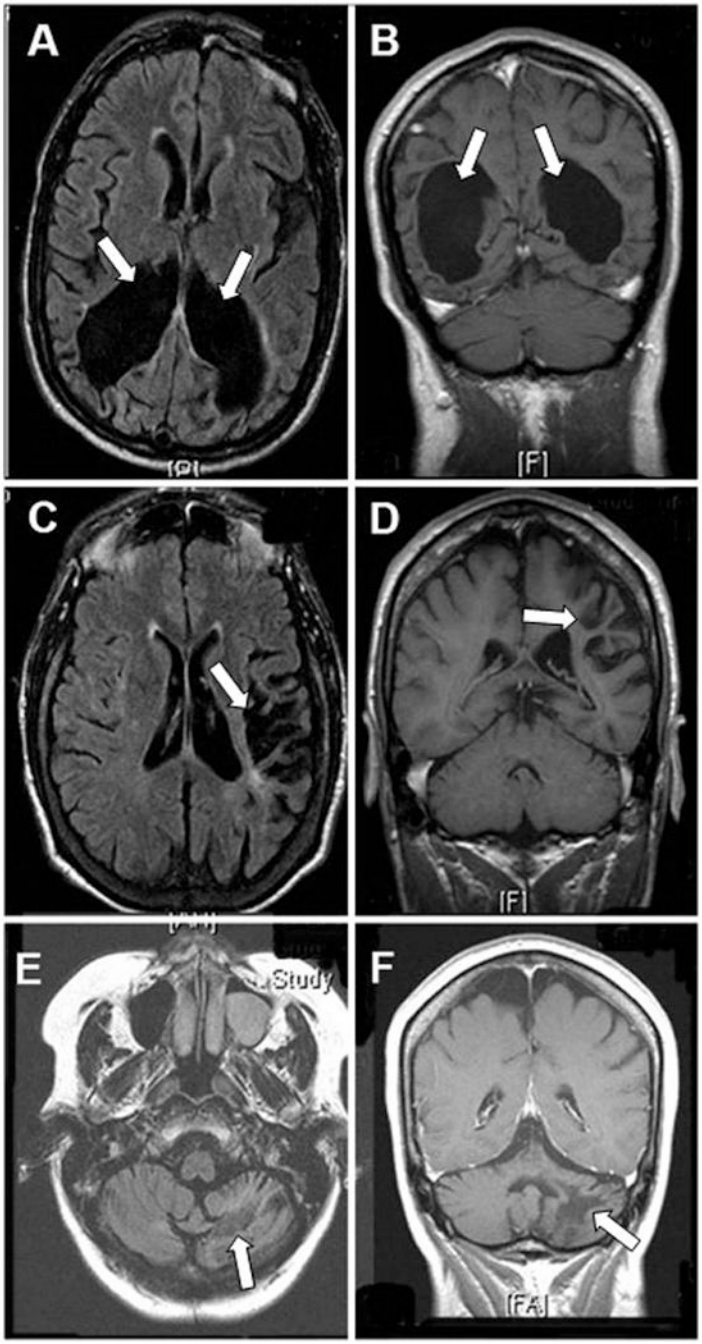

Figure 1.

Magnetic resonance imaging of chronic aspects of long survivors of PML: axial FLAIR (A) and coronal T1-weighted images (B) showing marked ventricular enlargement secondary to white matter destruction in the occipital lobes of patient # 10 (arrows) 11 years from onset of PML symptoms with preservation of the occipital gray matter. In patient # 24, there is focal left fronto-parietal subcortical atrophy in axial FLAIR (C) and coronal T1-weigted images (D) (arrows) with preservation of the cortical ribbon after 13 years of evolution. Patient # 6 has extensive destruction of the left cerebellar white matter 10 years from PML diagnosis with atrophy in axial FLAIR (E) and coronal T1-weighted images (F) (arrows). None of these chronic lesions enhanced after administration of gadolinium (not shown).

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Table 1

clinical characteristics and disability status of long term PML survivors

Patient	Age at onset	Treatment	Duration of disease (months)	Disability at time of PML diagnosis	Outcome (Modified Rankin Scale)
1	43	HAART	90	Bilateral pyramidal syndrome and impulsiveness	Stable (1)
2	38	HAART	113	Decreased visual acuity and executive functions	Partial improvement (1)
3	33	HAART + 5HT2A antagonist	75	Expressive aphasia and right upper extremity apraxia	Partial improvement (2)
4	45	HAART after four months of PML onset	78	Expressive aphasia, cognitive dysfunction, right pyramidal syndrome and sensory loss	Partial improvement (2)
5	44	HAART	84	Cognitive dysfunction, cerebellar syndrome	Marked improvement but developed seizures (1)
6*	54	ARA-C	188	Bilateral cerebellar syndrome	Partial improvement (3)
7	36	HAART + ARA-C + peptide T	149	Bilateral cerebellar syndrome	Stable (3)
8	35	HAART	162	Dysarthria and truncal ataxia	Partial improvement (2)
9	49	HAART	80	Bilateral cerebellar syndrome	Stable but developed seizures (4)
10	33	HAART	180	Bilateral cortical blindness	Stable but developed seizures (4)
11	40	HAART + 5HT2A antagonist	75	Abulia, transcortical aphasia, right homonymous hemianopsia and right pyramidal syndrome	Partial improvement but developed seizures (4)
12	33	HAART	83	Right pyramidal syndrome	Stable (2)
13	39	HAART + IFNα	79	Left pyramidal and cerebellar syndrome	Partial improvement (4)
14	34	HAART	74	Left pyramidal syndrome	Partial improvement (2)
15	37	HAART	150	Expressive aphasia	Marked improvement (1)
16	31	HAART	68	Seizures, left pyramidal syndrome, cognitive dysfunction	Marked improvement of cognitive and motor dysfunction, but developed seizures (1)
17	33	HAART	99	Cognitive dysfunction and a right sided sensory loss	Stable (1)
18	31	HAART+ IFNα	96	Expressive aphasia and cognitive dysfunction	Marked improvement of aphasia (1)
19	39	HAART+ IFNα	114	Cognitive dysfunction	Stable (3)
20	39	HAART	92	Right pyramidal syndrome and sensory loss	Stable (1)
21	41	HAART	105	Right cerebellar syndrome and dysarthria	Partial improvement (3)
22	36	HAART	162	Expressive aphasia and right pyramidal syndrome	Partial improvement of the aphasia (3)
23	31	HAART	162	Left cerebellar syndrome and dysarthria	Partial improvement of the cerebellar syndrome (2)
24	33	HAART + IFNα	186	Expressive aphasia and right pyramidal syndrome	Stable (4)

HAART: highly active antiretroviral therapy, INFα: interferon α 5HT2A: serotonin receptor 2A, ARA-C: cytarabine,

* HIV negative