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Inflammatory reaction in progressive multifocal leukoencephalopathy: Harmful or beneficial?

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Progressive multifocal leukoencephalopathy (PML) occurs in patients with profound immunosuppression. Although lesions are usually devoid of lymphoplasmocytic infiltrates, inflammatory forms of PML have been described, in both human immunodeficiency virus (HIV)-seropositive (HIV+) and -seronegative (HIV−) patients. In addition, PML has been shown to develop in HIV+ patients shortly after introduction of highly active antiretroviral therapy (HAART), despite a recovery of the immune system. Therefore, one could postulate that PML might arise in the context of an immune reconstitution syndrome. To examine the clinical and neuroradiological characteristics of inflammatory forms of PML, the authors performed a retrospective analysis of the patients seen at their institution since 1996 as well as a review of the literature. Of 39 HIV+ and HIV− PML patients, 5 (13%) presented with an inflammatory form of this disease. Two HIV+ patients developed PML soon after the onset of HAART, concomitant to immune recovery, as demonstrated by a decrease of HIV viral load (VL) and an increase of CD4+ T-cell count. Three patients (2 HIV+ and 1 HIV−) had signs of inflammation in the central nervous system (CNS) characterized by contrast-enhancing lesions on neuroimaging studies, and/or inflammatory infiltrates on brain biopsy. The presence of JC virus–specific cytotoxic T lymphocytes was demonstrated in 4/4 patients tested and the outcome was favorable in 3 of them. In agreement with previously published case reports, the data indicate that inflammatory reactions in PML are not infrequent, and that they are generally associated with a favorable prognosis. Therefore clinicians should not disregard the diagnosis of PML in presence of contrast-enhancing brain lesions, and should use caution before treating these immunosuppressed individuals with steroids. *Journal of NeuroVirology* (2003) **9(suppl. 1),** 25–31.

Keywords: cytotoxic T lymphocytes; HAART; HIV; immune reconstitution inflammatory syndrome; progressive multifocal leukoencephalopathy; steroids

Introduction

Progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the central nervous system (CNS) caused by the polyomavirus JC (JCV), occurs in patients with profound immunosuppression. Human immunodeficiency virus (HIV)-seropositive (HIV+) individuals, who represent the large majority of PML cases, are at risk of developing this disease when their CD4+ T-cell count drop below 200/μl. In 5% of HIV+ patients, JCV becomes reactivated and causes a lytic infection of oligodendrocytes. Despite a high

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level of replicating virus and extensive parenchymal damage in the CNS, PML lesions are conspicuously devoid of inflammation. Indeed, brain magnetic resonance imaging (MRI) usually shows no contrast enhancement in T1-weighted images, indicating an intact blood-brain barrier (BBB), and only a few inflammatory cells can be identified around PML lesions on histological studies.

In absence of a specific treatment for JCV, the main objective for physicians is to restore the competence of the immune system of their patients by treating the cause of their immunosupression. In HIV+ individuals with PML, this approach has been partly successful since the availability of highly active antiretroviral therapy (HAART) in 1996, which was associated with a rise in 1-year survival of these patients from 10% to 50% (Clifford *et al*, 1999; Gasnault *et al*, 1999; De Luca *et al*, 2000). Paradoxically, the incidence of PML has remained stable at approximately 5% despite the widespread use of HAART (Power *et al*, 2000), and the percentage of PML among HIV+ patients with focal brain lesions has not decreased (Ammassari *et al*, 2000). This is consistent with the observation that PML can still develop in patients treated with HAART (Tantisiriwat *et al*, 1999). This happens often in the context of an incomplete immunological and virological response to HAART as demonstrated by the persistence of low CD4+ T-cell count and elevated HIV viral load (VL). More surprisingly, however, PML has also been shown to develop in HIV+ patients soon after introduction of HAART, despite an increase of CD4+ T-cell count and a decrease of HIV VL (Kotecha *et al*, 1998; Mayo *et al*, 1998; Collazos *et al*, 1999; Cinque *et al*, 2001). These cases often have evidence of inflammation as demonstrated by contrast enhancement on MRI or lymphoplasmocytic infiltrates on brain biopsy (Berger *et al*, 1998; Kotecha *et al*, 1998; Collazos *et al*, 1999; Miralles *et al*, 2001). This has led authors to postulate that PML, like other opportunistic infections, could occur as an unexpected manifestation of immune reconstitution (Cheng *et al*, 2000; Cinque *et al*, 2001; Miralles *et al*, 2001; Shelburne *et al*, 2002). Immune reconstitution syndrome (IRS), also called immune restoration disease (IRD), or immune reconstitution inflammatory syndrome (IRIS), has been described in association with a variety of infectious pathogens. IRIS has been defined as a paradoxical deterioration in clinical status attributable to the recovery of the immune system, which is responsible for an inflammatory reaction at the site of a preexisting infection (Cheng *et al*, 2000; Shelburne *et al*, 2002). In HIV-seronegative (HIV◯) patients, IRIS can occur after discontinuation of immunosuppressive therapy. In patients with acquired immunodeficiency syndrome (AIDS), IRIS usually happens within a few weeks after the introduction of HAART, concomitant with an improvement of their immune status. It has been hypothesized that the stable incidence of PML compared to other CNS infections, which have decreased on HAART, might be due to IRIS (Cinque *et al*, 2001).

In the present study, we examined the clinical and neuroradiological characteristics of PML patients seen at our institution since 1996, who presented in the context of immune restoration, as ascertained by a rise in CD4+ T-cell count and a decrease of HIV plasma VL, or with signs of inflammation in the CNS documented by neuroimaging and/or brain biopsy. We review herein the literature on IRIS and PML and discuss this phenomenon in light of recent advances on the cellular immune response against JCV.

Results

Thirty-nine PML patients whose clinical outcome was known, including 31 HIV+ and 8 HIV◯ individuals, were diagnosed either by brain biopsy or by JCV DNA polymerase chain reaction (PCR) in the cerobrospinal fluid (CSF). Among these, 4 HIV+ and 1 HIV◯ patients fulfilled the inclusion criteria.

Patient 1

A 42-year-old man presented with Pneumocystis carinii pneumonia (PCP) heralding AIDS. His CD4+ T-cell count was 20/μl and his HIV VL was 264,000 copies/ml. He was started on d4T, ddI, and nelfinavir. Twelve weeks later, he presented with dizziness, blurry vision, and difficulty swallowing. His CD4+ T-cell count was 75/μl and his HIV VL had became undetectable. A brain MRI showed hyperintensities in T2-weighted images in the brain stem, the right superior colliculus, as well as in the left parietal lobe. CSF PCR was negative for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and JCV. Two months later, his HAART regimen was changed to AZT, efavirenz, indinavir, and ritonavir. Despite a negative PCR for JCV, the diagnosis of PML was retained as the most likely and the patient was started on cidofovir. Five months after the beginning of the symptoms, his neurological condition stabilized, and 4 months later, his CD4+ T-cell count was 198/μl and his HIV VL was still undetectable. At this time, PML was confirmed by a positive PCR for JCV in the CSF. Two years after the beginning of his disease, JCV VP1-specific cytotoxic T lymphocytes (CTLs) were detected in his PBMC.

Patient 2

A 34-year-old woman had been diagnosed with HIV infection 9 years earlier. She had a history of poor compliance to HAART. Her CD4+ T-cell count was 17/μl and her HIV VL was 28,000 copies/ml. She was started on abacavir, d4T, and nevirapine under close surveillance. Three weeks later, she presented with mental changes. A brain MRI showed left frontal and right parietal lesions without contrast enhancement and minimal mass effect. An MR spectroscopy revealed a decreased *N*-acetyl aspartate and increased choline in the regions of abnormal T2

signal, consistent with PML. This was confirmed by a positive CSF PCR for JCV DNA. Other opportunistic infections or tumors were ruled out. By then, her CD4+ T-cell count had risen to 74/μl and her HIV VL had become undetectable. A CTL assay performed 6 weeks after the beginning of her neurological symptoms revealed the presence of JCV VP1-specific CTLs in her peripheral blood mononuclear cells (PBMCs). She died 3 months after the onset of PML. An autopsy was not performed.

Patient 3

A 29-year-old man presented with progressive right-sided hemiparesis and aphasia. He was diagnosed with HIV infection and PML on the basis of clinical and neuroradiological findings. His CD4+ T-cell count was 287/μl. He was started on AZT, 3TC, and nevirapine and 2 months later, his HIV VL became undetectable. On this HAART regimen, he was clinically stable for 27 months. During this period, his CD4+ T-cell count progressively increased from 276/μl to 450/μl, and his HIV VL remained undetectable. He then presented with a subacute worsening of his neurological condition. A brain computed tomography (CT) showed a diffuse white matter process involving the whole left hemisphere with moderate mass effect and midline shift as well as patchy contrast enhancement of the lesions. The patient was started on dexamethasone, topiramate, and cidofovir at another hospital. A brain MRI, performed 3 days later, showed that the contrast enhancement had disappeared. Six weeks later, a CTL functional assay demonstrated the presence of JCV VP1-specific CTLs in his PBMCs. The diagnosis of PML was later established by a positive PCR for JCV in the CSF. Other opportunistic infections or tumors of the CNS were ruled out. His neurological symptoms improved gradually and he returned to his clinical baseline. The MRI showed regression of the left hemispheric edema. He remains stable more than 2$^1/_2$ years after this inflammatory episode.

Patient 4

A 40-year-old man presented with mental slowness, speech disturbances, difficutly swallowing, and increasing weakness of the lower extremities. He had been diagnosed 8 years ago with HIV, and his compliance to HAART was poor. At the onset of his neurological symptoms, his CD4+ T-cell count was 298/μl and his HIV VL was more than 100,000 copies/ml. A brain MRI revealed multifocal lesions of different sizes, predominating at the gray-white matter junction in the left temporal lobe and in the frontal lobes. Several of these lesions were enhancing after contrast administration (Figure 1). A PCR for JCV DNA in the CSF was positive, establishing the diagnosis of PML. Other opportunistic infections or tumors were ruled out. HAART, consisting of d4T, 3TC, and lopinavir/ritonavir was continued, but subsequently under close supervision. A second brain MRI, performed 2$^1/_2$ weeks after the first one showed an increase in the size of the lesions, but a decrease in the contrast enhancement. Four months after the beginning of the symptoms, his CD4+ T-cell count was

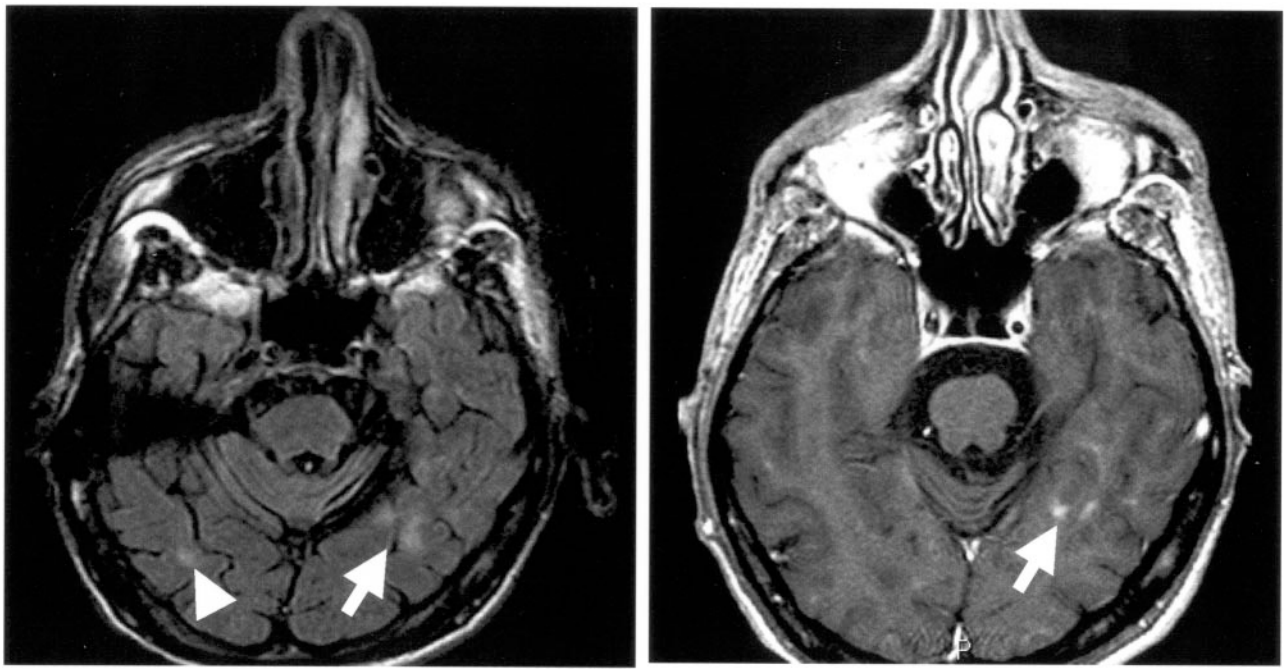

Figure 1 Contrast enhancement of PML lesions. A left temporal lobe lesion seen in FLAIR (*arrow, left panel*) enhances after gadolinium injection in T1-weighted image (*arrow, right panel*), whereas a right temporal lobe lesion is only detected in FLAIR sequence (*arrowhead, left panel*).

Table 1 Clinical and immunological data of 5 patients with inflammatory forms of PML

Patient	*HIV status*	*CNS signs of inflammation*	*Time between HAART and PML*	*HIV VL in copies/ml*	*CD4+ T-cell count/μl*	*JCV-specific CTL (no. of weeks after PML onset[a])*	*Outcome since PML onset*
1	Positive	Absent	12 weeks	<50 ↓	75 ↑	+ (104)	Alive and stable after 3 years
2	Positive	Absent	3 weeks	<50 ↓	74 ↑	+ (6)	Death in 3 months
3	Positive	Enhancement+ Mass effect+	>1 year	<50	450	+ (6)	Alive and stable after 6 years
4	Positive	Enhancement+	1 year, but poor compliance	>100,000	298	Not tested	Death in 5 months
5	Negative	Enhancement+ Biopsy+	n/a	n/a	n/a	+ (18)	Improved but died of unrelated condition after 6 months

HIV VL and CD4+ T-cell count are indicated at the time of PML onset. The direction of the arrow indicates an increase or decrease compared to previous values. Enhancement +: presence of contrast enhancement on neuroimaging. Mass effect +: presence of mass effect on neuroimaging. Biopsy +: presence of perivascular inflammatory infiltrate on brain biopsy. [a]Number of weeks between PML onset and the first CTL assay.

221/μl and his HIV VL was 21,000 copies/ml. He died 1 month later.

Patient 5

This HIV-negative 80-year-old woman with a history of a low-grade B-cell lymphoma presented with severe cognitive dysfunction, aphasia, and gait apraxia. A brain MRI showed bilateral hemispheric white matter lesions with a faint rim of contrast enhancement. A CSF examination was normal. A brain biopsy ascertained the diagnosis of PML and revealed the presence of a mixed perivascular inflammatory infiltrate. The patient did not receive any specific treatment but improved dramatically from a neurological standpoint during the next 6 months. Four and a half months after the beginning of her symptoms, a CTL assay was performed and revealed the presence of JCV VP1-specific CTLs in her PBMCs. Unfortunately, she passed away due to a sepsis caused by an unhealed decubitus ulcer.

The five cases reported here illustrate the fact that inflammatory forms of PML can occur in various clinical settings (Table 1).

Discussion

In IRIS, the clinical worsening is temporally related to the recovery of the immune system and is due to the development of an inflammatory response directed against infectious pathogens or antigens. Classical manifestations of IRIS in AIDS include CMV retinitis and uveitis, mycobacterium avium complex lymphadenitis, and cryptococcal meningitis. For mycobacterial and fungal infections, the median interval between the introduction of HAART and the onset of IRIS is 11 days, whereas it is 42 days in the cases of viruses such as CMV or hepatitis B virus (HBV) (Cheng *et al*, 2000).

Atypical cases of PML with an inflammatory component have been previously described. In 1975, before the AIDS era, Richardson *et al* noted that some PML patients had mononuclear inflammatory infiltrates in their CNS lesions. Interestingly, these patients had a more benign clinical evolution with longer survival than those without inflammation (Richardson and Johnson, 1975). This observation was confirmed by others (Schlitt *et al*, 1986; Zochodne and Kaufmann, 1987). In the pre-HAART era, Hair *et al* described numerous inflammatory cells in PML lesions in three cases of PML, heralding AIDS. One did not receive any treatment and two were treated with AZT. They all had a favorable outcome with prolonged survival compared to cases with less inflammation (Hair *et al*, 1992). In the beginning of the HAART era, Berger *et al* described favorable prognostic factors including (1) PML heralding AIDS, (2) a CD4+ T-cell count of 300/μl or higher at onset, and (3) contrast-enhancing PML lesions on neuroimaging (Berger *et al*, 1998). These criteria suggest that PML carries a better prognosis when there is relative preservation of the host immunity associated with an inflammatory response in the CNS. Very rarely, PML can be associated with mass effect without contrast enhancement (Finelli, 1998). In one patient, it was associated with prolonged survival (Thurnher *et al*, 2001), whereas it produced a midline shift and subfalcine herniation in another who had a fatal outcome (Koralnik, 2002).

There have been few reports of PML occurring as a possible manifestation of IRIS in AIDS. Mayo *et al* described three cases of HIV+ patients who developed PML during the first weeks of HAART. Two of them had PML onset 5 and 8 weeks after the introduction of HAART, when their CD4+ T-cell counts were above 300/μl (Mayo *et al*, 1998). In another report, 4 patients, including the 2 aforementioned, had contrast-enhancing PML lesions on MRI (Collazos *et al*, 1999). Another HIV+ patient developed contrast enhancing PML lesions after the introduction of HAART. A brain biopsy revealed an extensive demyelination with surrounding inflammation

consisting of lymphoplasmoid cells, including CD8+ T cells (Kotecha *et al*, 1998). In all the patients described in these reports, the outcome was favorable. By contrast, Miralles *et al*, have reported clinical and radiological worsening in 3 HIV+ patients with established PML soon after onset of HAART, despite a good immunological and virological response. On brain biopsy, there was a marked perivascular lymphoplasmocytic infiltrate, characterized mostly by CD8+ T cells and CD20+ B cells. Two patients were treated with steroids, one died, one survived and a third was lost to follow-up. The same authors analyzed retrospectively the brain biopsies of 28 PML patients and found inflammatory changes in 4/9 patients treated with HAART, but only in 1/19 HAART-naïve patients (Miralles *et al*, 2001). Cinque *et al* reported that PML developed within 9 weeks after initiation of HAART in 5/27 HIV+ patients (18%) while there was a reconstitution of their immune function (Cinque *et al*, 2001).

Of the 31 HIV+/PML patients evaluated in the present study, 2 (6.5%) developed PML shortly after the initiation of HAART while their immunologic parameters were improving, as demonstrated by a rise in CD4+ T-cell count and a decrease in HIV VL (patients 1 and 2). Interestingly, their MRI did not show contrast enhancement. However, this feature is usually transient and could, therefore, easily be missed. Of the 39 HIV+ and HIV◯ PML patients evaluated, 3 (7.7%) had contrast enhancement on the neuroimaging studies (patients 3, 4, and 5), which was probably due to CNS inflammation, as revealed by a brain biopsy in 1 patient (patient 5). The presence of JCV-specific CTL could be tested and demonstrated in 4 patients (patients 1, 2, 3, and 5). Among these, patient 1 and 5 were tested for the presence of JCV-specific CTLs 2 years and $4^1/_2$ months in the course of their disease. Therefore, causality between the development of a cellular immunity and stabilization of PML could not be established. Patient 3, however, had detectable CTLs already 6 weeks after disease onset, and improved clinically. This is consistent with the notion that the development of a specific immune response against JCV is usually associated with a favorable outcome (Du Pasquier *et al*, 2001; Koralnik *et al*, 2001, 2002). By contrast, patient 2 died despite the presence of JCV-specific CTLs early in the disease. She had PML, which had occurred 3 weeks after the initiation of HAART while she had a decreasing HIV VL, rising CD4+ T-cell count, and detectable JCV-specific CTLs. Despite improvement of these immunological parameters, her disease continued to progress and she died after 3 months. It is unclear whether in this patient the immune response itself was harmful, or whether it did not have time to deploy its effects in the brain, as suggested by the absence of contrast enhancement in PML lesions. Patient 4 had a fatal outcome in 5 months, despite an inflammatory response in the brain, as suggested by contrast enhancement on MRI. He died before a CTL assay could be performed. It appears that an inflammation in this case was not efficient to prevent disease progression. However, patients 1, 3, and 5 improved in the context of an inflammatory response demonstrated either by JCV-specific CTLs in the peripheral blood or/and by contrast enhancement on MRI. Among them, only patient 3 had significant enough CNS mass effect and midline shift to require treatment with steroids.

There is now a growing body of evidence showing that an inflammatory response can be present in PML, and it often occurs in the setting of immune recovery. This has been associated with a favorable prognosis in most (Richardson and Johnson, 1975; Schlitt *et al*, 1986; Zochodne and Kaufmann, 1987; Hair *et al*, 1992; Berger *et al*, 1998; Kotecha *et al*, 1998; Collazos *et al*, 1999) but not all studies (Cinque *et al*, 2001; Miralles *et al*, 2001). Inflammatory infiltrates seen in the brain of these patients were mostly CD8+ T cells and CD20+ B cells. We have independently demonstrated that survivors of PML have detectable JCV-specific CD8+ CTLs in their PBMCs, whereas patients who are unable to mount this cell immune response usually have a rapid fatal outcome. In patients 3 and 5 of the present series, contrast enhancement and/or CNS infiltrates correlated with the presence of JCV-specific CTLs in the peripheral blood. We therefore postulate that JCV-specific CTLs, which are able to recognize and destroy JCV-infected glial cells, are responsible for the inflammatory response seen on MRI and histology, and are instrumental in the prevention of disease progression.

If CTLs are responsible for the CNS inflammation in PML lesions and have a protective role, why does PML occur in the first place in the context of HAART-induced immune recovery, and could this be a true manifestation of IRIS? The concept of IRIS would imply a latent subclinical infection of glial cells by JCV, with expression of JCV early T protein, but interruption of the lytic cycle preventing the expression of the capsid proteins and virion assembly. Upon immune recovery, JCV-specific CTLs helped by CD4+ T cells would unravel a latent infection, which would otherwise have remained dormant, and create symptomatic inflammation of the CNS. This one would be detrimental to the patient and should be treated with steroids. In support of this hypothesis, Quinlivan *et al* have found JCV DNA by PCR in 4/13 HIV+ individuals without PML (Quinlivan *et al*, 1992). In addition, Mori *et al* found JCV DNA by *in situ* hybridization in the brain of 4/10 elderly patients without PML and without known immunosupression (Mori *et al*, 1991). However, the mere presence of viral DNA could not in itself trigger an immune response, and JCV antigens have not been detected outside of PML lesions. Moreover, a block in the lytic cycle of JCV has not been documented in immunosuppressed individuals. Thus, a latent subclinical infection of the CNS by JCV appears unlikely.

It is also possible that PML occurring shortly after the introduction of HAART be due to cytokine-mediated mechanisms. Decreasing levels of interferon (IFN)-μ and interleukin (IL)-12 have been implicated in increasing hepatitis C virus (HCV) viremia and cryptococcal meningitis, respectively (DeSimone *et al*, 2000). By analogy, one can postulate that after the introduction of HAART, HIV VL decreases, which in turn will lower the levels of cytokines, thus promoting JCV reactivation. This reactivation may occur either at the level of a latent CNS infection by JCV or involve peripheral reservoirs of the virus such as the kidneys or lymphoid organs.

Another scenario invokes a productive, yet subclinical infection of oligodendrocytes by JCV, occurring incidentally around the time of HAART onset. As reconstitution of the immune system can take up to several months, PML may still become clinically apparent but an improved immune function leads to an inflammatory response that is beneficial and may eventually prevent disease progression. In this context, treatment with steroids is not indicated and could even be detrimental to the patient.

If this scenario is correct, why do some patients still present with worsening neurological symptoms, and why do some succumb to PML despite this inflammatory response? When considering the clinical outcome of PML, several parameters have to be taken into account, including timing of HAART onset, compliance to treatment, size and location of PML lesions, JCV VL in CSF (Taoufik *et al*, 1998; Koralnik *et al*, 1999; Yiannoutsos *et al*, 1999; Antinori *et al*, 2001), and the structure of JCV regulatory region (Pfister *et al*, 2001), which may be independently associated with disease evolution. Therefore, the development of an immune response against JCV occurring too late may not be sufficient to prevent an initial worsening of PML and a fatal outcome in some patients.

The theoretical debate described above leads to more practical issues: Should clinicians give steroids to patients who develop inflammatory PML after onset of HAART? Current data do not support the hypothesis of a widespread restricted infection of glial cells by JCV waiting to become the innocent target of a recovering immune system. Moreover, the inflammatory response is rarely associated with significant edema and mass effect, which would require steroids to prevent herniation. Finally, the majority of inflammatory PML cases appear to have a favorable outcome. A prospective study is in progress in our institution to follow JCV-specific immune response of these patients since the onset of PML. For the time being, clinicians should use caution before treating these immunosuppressed individuals with steroids in the absence of clinical or radiological signs of impending brain herniation.

Material and methods

The detection of JCV-specific CTLs was performed as previously reported (Koralnik *et al*, 2001, 2002).

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