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Progressive multifocal leukoencephalopathy in an HIV patient receiving successful long-term HAART

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Abstract Progressive multifocal leukoencephalopathy (PML) has been traditionally associated to severe immunosuppression and described mainly in highly active antiretroviral therapy (HAART)-naïve patients with a low lymphocyte CD4+ count. In the last years, some cases of PML have been described in HIV patients with a higher CD4+ count shortly after initiation of HAART and in association with the immune reconstitution inflammatory syndrome (IRIS). We report on a rare case of PML, not IRIS associated, that occurred in a HIV-positive patient with a lymphocyte CD4+ count greater than 700/μl and with an undetectable HIV viral load resulting from a long-term HAART. We describe the pathological and the ultrastructural features of the brain lesion. This case confirms that a severe immunosuppression or an IRIS is not required for the development of PML in HIV positives. The diagnosis of PML should always be considered in patients with consistent neurological symptoms, even with a high lymphocyte CD4+ level and a full viral suppression resulting from a long-term HAART.

Keywords Progressive multifocal leukoencephalopathy · HIV · JC virus · HAART

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a relevant clinical problem in terms of morbidity and mortality in HIV-positive patients even in the HAART era. The introduction of HAART has been followed by a decreased incidence of HIV-related PML and by prolonged survival of patients. Recent studies suggest that only 0.6% of HAART-treated patients ultimately develop PML. This is significantly lower than earlier estimates of 4–5% in the pre-HAART era (Khanna et al. 2009a). However, the decrease in the incidence of PML has been less marked than the reduction of other HIV-related opportunistic disease of the CNS (Cinque et al. 2009). PML has been traditionally associated with severe immunosuppression and described mainly in HAART-naïve patients with low CD4+ count. More recently, cases of PML have been observed in patients with a higher CD4+ count shortly after initiation of HAART, in association with the immune reconstitution inflammatory syndrome (IRIS; Falcò et al. 2008). Herein we report on a rare case of PML, not IRIS-associated, that occurred in a HIV-positive patient with a normal CD4+ cell count and an undetectable HIV viral load resulting from a long-term HAART. We describe the pathological and ultrastructural features of brain lesion.

Case report

The patient, a 46-year-old Italian female, was infected with HIV-1 since 2001. On October 2003, she started HAART with abacavir, lamivudine and zidovudine without prior AIDS-defining conditions.

Her CD4+ count nadir was 244/μL. Over the following years, the HIV viral load remained constantly undetect-

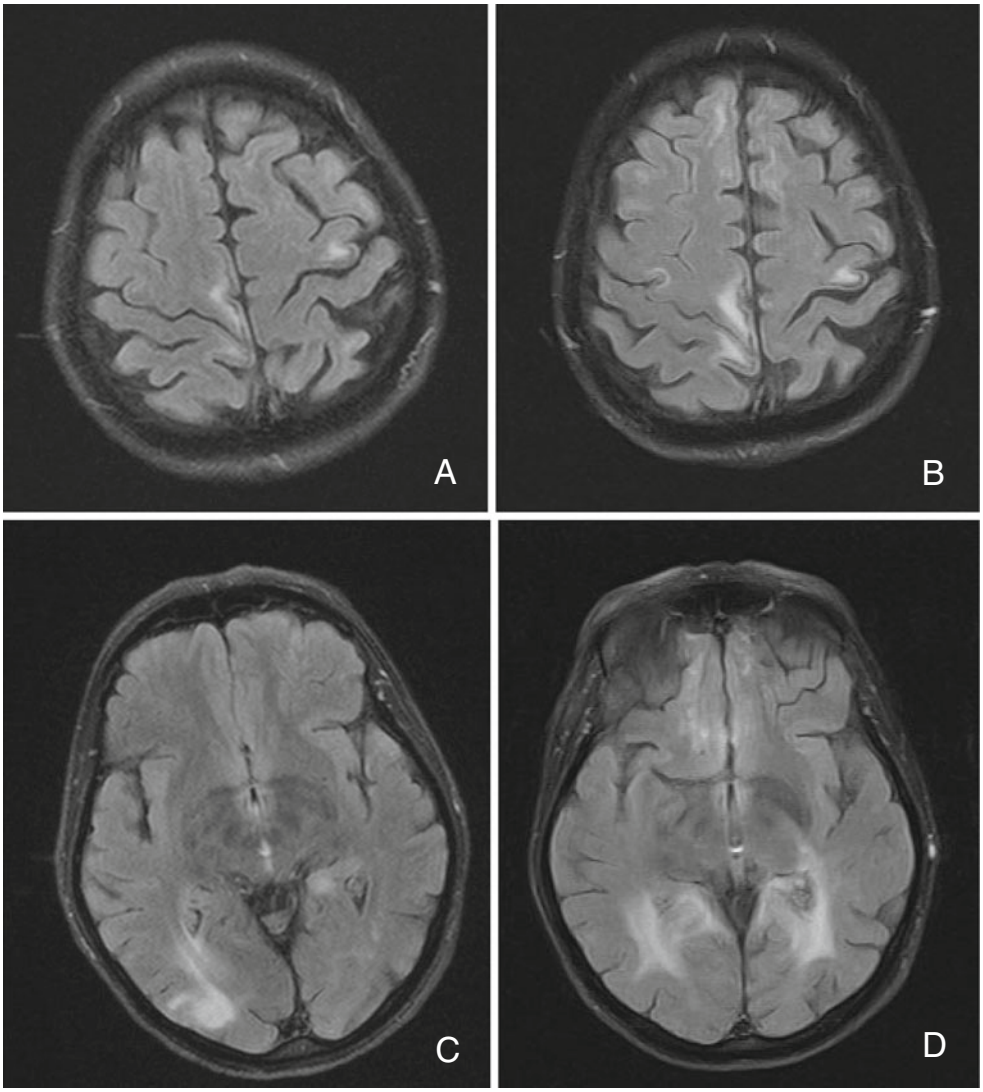

Fig. 1 Fluid attenuation recovery MRI 2 months (**a**, **c**) and 10 months (**b**, **d**) after the onset of symptoms

able and the CD4+ count >700/μL. On February 2008, she developed rhythmic focal motor seizures in her right wrist. Her total lymphocyte count was 4,204/μL, the CD3+ count was 3,624/μL (range 841–1,642), the CD4+ count was 752/μL and the CD8+ count was 2,682/μL (range 301–607).

Magnetic resonance imaging (MRI) of the brain showed multiple subcortical T2-weighted hyperintensities involving

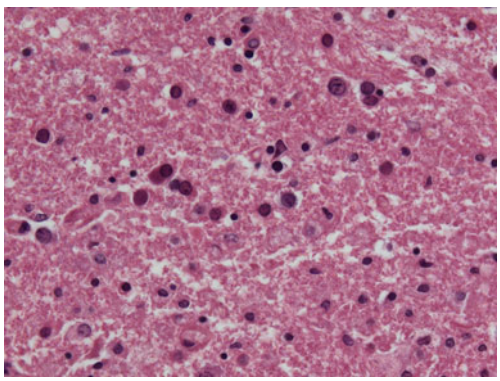

Fig. 2 Area of demyelination showing enlarged oligodendrocytes with basophilic nuclei, foamy macrophages and a bizarre astrocyte (haematoxylin–eosin, original magnification ×100)

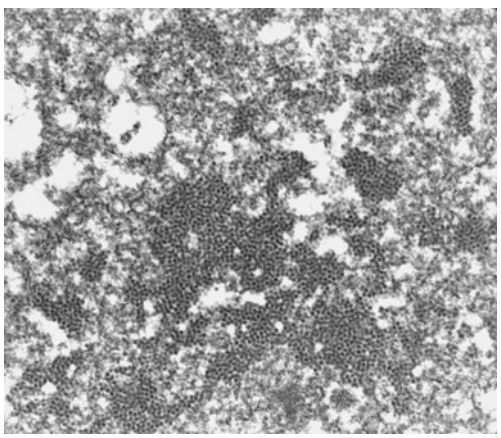

Fig. 3 Oligodendrocyte nucleus containing "para-crystalline" polyomavirus particles (electron micrography, OM ×12,000)

the left frontal, parietal and temporal lobe. There was no mass effect or contrast enhancement on T1-weighted images. Two months later, she developed focal motor seizures of the left ankle, low limb weakness and left hemianopsia, hyperreflexia of the left leg and left Babinski's sign. The brain MRI showed the new onset of hyperintensity in the right occipital white matter (Fig. 1a and c). Cerebrospinal fluid (CSF) analysis showed normal cytochemistry and increased immunoglobulins G production; cultures for bacteria, fungi and mycobacteria, CSF PCR for JC virus (JCV), toxoplasma gondii, cytomegalovirus, herpes simplex, varicella-zoster and Epstein–Barr virus were negative. The CSF HIV-RNA, the cytology and cytofluorimetry were negative. The patient progressively worsened; she developed numbness of the right arm, gait imbalance and slurred speech. A second analysis of the CSF detected JCV sequences, suggesting the diagnosis of PML.

JCV DNA was detected by PCR using JCV-BKV Oligomix Alert Kit (Nanogen Advanced Diagnostics, Turin, Italy) that allows distinction between JCV and BKV (Ferrante et al. 1995). Owing to the good CNS penetration rank and the undetectable blood and CSF viral level, the HAART was not modified. Despite the HAART and the intravenous steroid treatment, her condition dramatically deteriorated. In December, she was bedridden with an altered level of consciousness and decorticated posturing.

A brain MRI showed that the T2 hyperintense lesions had progressed in cerebral and brainstem white matter (Fig. 1b and d). One year after the onset of symptoms, she died from nosocomial pneumonia. Her CD4+ count was 1,044/μL, the HIV viral load was undetectable. Post-mortem examination of the brain showed numerous multiple irregular foci of demyelination, frequently confluent, involving cerebral, cerebellar and brainstem white matter. The major lesions contain large collections of foamy macrophages and were characterized by central necrosis. Only scanty perivascular lymphocytes were present. In the periphery of lesions, we observed very large bizarre astrocytes and oligodendrocytes with enlarged nuclei containing viral inclusions, ultrastructurally consistent with polyomavirus-like particles (Fig. 2). Viral, bacterial and parasitic co-infections were excluded by pathologic examination. The histological and electron microscopy features confirmed the diagnosis of PML (Fig. 3).

Discussion

The clinical manifestation of PML varies depending on the affected area of the CNS; however, the most common presentation includes a broad spectrum of focal neurological deficits such as hemiparesis or visual impairment, gait disturbances, dysarthria, cognitive dysfunction and sensory deficit (Tan and Koralnik 2010). In our patient, the neurological sign of onset consisted in focal motor seizures probably due to motor cortical involvement from adjacent demyelinating lesions. This presentation is unusual but previously described in PML-affected subjects (Ferrari et al. 1998). In recent years, PML has been observed in patients receiving HAART, in the setting of IRIS that enhances the perivascular inflammatory infiltration. In these patients, the role of corticosteroids is a matter of debate, since there is no demonstration that they are indeed beneficial (Berger 2009). In our case, the absence of recent restoration of immune response, the absence of contrast enhancement of demyelinating lesions in the brain MRI and the scanty inflammatory infiltration in pathological study all ruled out the possibility of PML-IRIS. Moreover, no other conditions of minimal or occult immunosuppression, described as being associated with PML in HIV negatives, were identified in this case (Gheuens et al. 2010).

It is of interest that our patient developed a PML despite a long-term successful HAART that is helpful to restore the host ability to control the JCV infection. The presence of JCV-specific T cell response has been associated with a favourable outcome and a prolonged survival in PML-affected patients (Du Pasquier et al. 2004; Khanna et al. 2009b). It is possible that our patient did not restore the specific JCV immunological response despite the long-term HAART.

Several aspects in this case: the high CD4+ T count, the undetectable HIV viremia, the long-term HAART and the initially negative JCV PCR on CSF were highly misleading for establishing the diagnosis of PML. Cases of PML in patients with an high CD4+ count have been described in HAART-naïves or in patients receiving HAART but at variance with our case, without a full virological response (Berger et al. 1998; Tantisiriwat et al. 1999; Cinque et al. 2003). Our patient developed aggressive PML despite a CD4+ count >700/μL and a suppressed systemic and CSF viral load and in absence of MRI and histological signs of IRIS. This case confirms that a severe immunosuppression or an IRIS is not required for the development of PML in HIV positives.

In conclusion, the diagnosis of PML should always be considered in patients with consistent neurological symptoms, even with high CD4+ level and a full viral suppression resulting from a long-term HAART.

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