Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment

C Hoffmann, H-A Horst, H Albrecht, W Schlote

A case of biopsy verified progressive multifocal leucoencephalopathy (PML) in an HIV patient is presented. Imaging and histological examination confirmed remarkable inflammatory activity accompanied by an unusually benign clinical course despite no clear evidence of immune reconstitution after the start of antiretroviral treatment. This case not only raises several questions regarding the pathophysiology of PML, but gives also evidence that AIDS associated inflammatory PML must be considered another clinical entity in the expanding range of diseases now commonly referred to as the immune reconstitution syndrome.

Progressive multifocal leucoencephalopathy (PML) is a demyelinating disease of the central nervous system. It is caused by the JC virus (JCV), a human polyomavirus replicating in human glial cells. PML is the result of the reactivation of latent JCV infection, usually in the setting of cellular immunodeficiencies. Cases associated with the HIV account for up to 85% of all cases. Pathological findings include lytic infection of myelin producing oligodendrocytes. Perivascular inflammation is usually absent. Usually, the clinical outcome of patients with PML is poor with an inexorable progression to death within six months of symptom onset. Experimental treatments such as cytarabine, camptothecin, interferon, or cidofovir have either failed to show any clinical benefit or their efficacy remains to be confirmed by randomised trials. In a cohort of HIV infected patients with recorded PML we have previously shown that some of these patients may derive a significant survival benefit from highly active antiretroviral therapy (HAART). Immune recovery after the start of HAART, however, does not inevitably result in clinical improvement of PML nor does it necessarily confer reliable protection against this disease in HIV infected patients. In this report we present a case of biopsy verified PML that presented unexpected histopathological findings and an unusually benign clinical course despite no clear evidence of immune reconstitution after the start of HAART.

CASE REPORT

A 51 year old homosexual man was diagnosed HIV-1 positive in 1985. Until 1998, his CD4 cell counts remained above \(10^6\) cells/l. After gradual depletion of the CD4 counts, the patient was referred to the outpatient clinic of the University of Kiel in July 1999. He was naive to antiretroviral drugs and in general good health. Routine laboratory testing revealed significant HIV plasma viraemia (454,800 RNA copies/ml, Roche-Amplicor, Basle, Switzerland), a CD4 cell count of \(174 \times 10^6\) cells/l (12%) but no other abnormalities. HAART using stavudine, didanosine, and nelfinavir was started. Four weeks later, HIV-RNA had decreased to 3200 copies/ml whereas CD4 cell count had failed to increase (147 \(\times 10^6\) cells/l and 14% respectively). After this follow up visit the patient’s condition began to deteriorate. He suffered from low grade fever as well as progressively impaired memory and cognition.

Abbreviations: PML, progressive multifocal leucoencephalopathy; JCV, JC virus; HAART, highly active antiretroviral therapy

Figure 1 Cranial magnetic resonance images of the brain with T1 weighted image (A) and fluid attenuated inversion recovery pulse sequence (B) with signal abnormalities in the brachium cerebellum.
dizziness, ataxic gait, and blurred vision. Paresis or sensory deficits were notably absent. Cranial magnetic resonance imaging revealed hyperintense signal abnormalities on T2 weighted images and fluid attenuated inversion recovery pulse sequence predominantly located in the cerebellum and occipital lobes. The lesions showed moderate perifocal gadolinium enhancement (fig 1). Analysis of cerebrospinal fluid was significant for a slightly increased cerebrospinal fluid protein (72 mg/dl, normal range 15–45) and a mild pleocytosis (22 WBC cu/mm, normal range 0–10) but was otherwise non-diagnostic including negative polymerase chain reaction for mycobacteria, fungi, and herpes viruses. No organisms. Specifically, no toxoplasma pseudocysts or tachyzoites were observed. These infiltrates were predominantly seen in perivascular spaces (fig 2). No mature granulomata were visualised and the inflammatory infiltrations did not contain either epitheloid or multinucleated giant cells.

Specimens from an occipital lesion showed widespread and diffuse mononuclear inflammatory infiltration of brain tissue throughout cortex and subcortical white matter. Areas of more focal infiltration consisting of LCA positive small and medium sized lymphocytes and some plasma cells were observed. These infiltrates were predominantly seen in perivascular spaces (fig 2). No mature granulomata were visualised and the inflammatory infiltrations did not contain either epitheloid or multinucleated giant cells. No necrotic areas were found.

In situ hybridisation with a JCV probe (prepared by nick translation of a clone of the entire JCV genome, Enzo Diagnostics, Farmingdale, NY, USA) revealed a strong positive reaction in many of the nuclei of the scattered large round glial cell, presumably representing oligodendrocytes (fig 3). There was no indication of other infectious agents or microorganisms. Specifically, no toxoplasma pseudocysts or tachyzoites and no fungal elements were identified on PAS and Grocott stains.

After treatment interruption of three weeks, HAART was restarted. During the ensuing weeks the patient’s neurological symptoms not only stabilised but began to improve. Three years after symptom onset no focal neurological deficits remain. Tests of higher cognitive functions revealed no abnormality with the exception of a mild change in handwriting. In the meantime the patient has resumed full time work. Repeated MRI showed a slow but gradual regression of the lesions and of contrast enhancement. Viral load and lymphocyte subsets continue to display a discordant response to HAART. Whereas viral load has remained below the detection limit of the ultra sensitive assay (<25 copies/ml) for more than two years, CD4 cells counts did not increase significantly. At the last follow up, CD4 count was 232×10^6 cells/l (14%).

**DISCUSSION**

This unusual case raises several questions regarding the pathophysiology of PML. Firstly, the onset of PML shortly after the start of HAART was unexpected. There are only a few reports of PML occurring shortly after beginning HAART. Similar to our patient, in some of these cases a prominent perivascular inflammatory infiltration consisting mainly of T lymphocytes and monocytes/macrophages was identified. The inflammatory response probably accounts for the unusual contrast enhancement observed in these patients. These findings led to the speculation that inflammatory PML is characteristic of patients experiencing immune reconstitution of their CD4 cell counts during the first weeks of HAART. In the case presented, this was obviously not the case, as the patient’s CD4 count failed to increase significantly despite a sustained virological response.

Such discordant responses have been observed in HIV subjects without PML. This phenomenon is more common in older persons, presumably secondary to more advanced thymic insufficiency. As the immune deficiency of HIV infection, however, is both quantitative and qualitative, it is not known how much and what kind of immune restoration is needed to achieve antigen specific immunocompetence. The remission in our case may be partially explained by reconstitution of JCV specific T cell reactivity. Additionally, compared with most PML patients, our patient had a comparatively preserved CD4 count, which may have facilitated the inflammatory response against JCV. Comparatively high CD4 counts at disease onset have previously been identified as predictive of prolonged survival in PML patients.

The possibility of other concurrent disorders was thoroughly investigated but no evidence of coexisting HIV encephalitis, toxoplasmosis, tuberculosis, fungal infections, infections with any of the neurotropic herpes viruses, or sarcoidosis was detected on special stains or culture. The available evidence strongly favours JCV as the only pathogen responsible for the observed pathology.

The patient’s HIV viral load may also have contributed to the observed outcome. The HIV-1 encoded transregulatory protein, Tat, has been shown to upregulate the JCV lytic cycle in vitro. Although HIV and JCV affect different cerebral cells, there is evidence that both viruses may also interact in vivo. A recent study of brain tissue of AIDS patients with PML demonstrated an accumulation of Tat in JCV infected oligodendrocytes. Accordingly, the reduced HIV replication in the brain may have resulted in a down regulation of the transcriptional activity of JCV in our patient. This is consistent with the observation that subjects with PML on HAART that achieve a viral load of less than 500 copies/ml have a significantly longer survival.
Finally, the dramatic clinical improvement observed in our patient must be considered remarkable. Except for a mild change in handwriting, our patient was in complete clinical remission more than 2.5 years after onset of symptoms.

In conclusion, inflammatory PML is another clinical entity in the expanding range of diseases now commonly referred to as the immune reconstitution syndrome. This case also demonstrates that in the era of highly active antiretroviral therapy, PML may not only manifest atypical pathological and radiological features, but may also lose its relentless character—even in the absence of a significant increase of the CD4 cell counts.

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Received 27 September 2002
Accepted in revised form 10 February 2003

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J Neurol Neurosurg Psychiatry 2003 74: 1142-1144
doi: 10.1136/jnnp.74.8.1142

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