Progressive Multifocal Leukoencephalopathy Presenting as IRIS in an AIDS Patient

A Case Report and Literature Review

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SUMMARY – *Progressive multifocal leukoencephalopathy causes an infection of the central nervous system by JC virus (JCV), a polyomavirus that destroys oligodendrocytes and their myelin processes. Here, we describe a patient with AIDS who developed a progressive multifocal leukoencephalopathy with the clinical and neuroimaging characteristics of the immune inflammatory reconstitution syndrome. Unlike other opportunistic infections, this disease can present when CD4 T cell counts are higher than those associated with AIDS and also when patients are receiving combined antiretroviral therapy. Clinical suspicion of this form of the disease is based on clinical examination that shows focal neurological deficits associated with magnetic resonance images findings. The histopathological examination of brain biopsy smears and the identification of JCV in cerebrospinal fluid or brain tissue are definitive for the diagnosis.*

Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic subacute demyelinating infection of the central nervous system (CNS) first described by Åstrom et al. in 1958¹. The etiological agent is a DNA polyomavirus, called JC virus (JCV) with tropism for oligodendrocytes and myelin protein. Before the pandemic of AIDS, PML was a rare disease, but it now occurs in up to 7% of these patients without combined antiretroviral therapy (ART)².

The classic clinical presentation of PML includes subacute to chronic focal neurological deficits depending on the location of the lesions. The typical magnetic resonance imaging (MRI) findings of PML are white matter lesions in different brain areas, predominantly the parieto-occipital lobes. They are usually hyperintense in T2-weighted and FLAIR sequences and hypointense in T1-weighted scans in relation to the white matter involvement, without contrast enhancement and no mass effect³. However, a small proportion of patients

present the inflammatory form of the disease defined radiologically by the presence of contrast enhancement, perilesional edema and mass effect on the middle line structures⁴.

We describe an AIDS patient who developed an unusual form of PML presenting as an immune inflammatory reconstitution syndrome (IRIS) with a brain cerebral mass lesion at MRI.

Case Report

A 29-year-old heterosexual man was referred to the Infectious Diseases Department at F.J. Muñiz Hospital with a three-month history of headache and generalized tonic-clonic seizures. He had a diagnosis of HIV infection when he developed *Pneumocystis Jirovecii* pneumonia and disseminated cryptococcosis. He completed therapy with cotrimoxazol and amphotericin B and was started on AZT/3TC/atazanavir/ritonavir and secondary prophylaxis with cotrimoxazol three times weekly and fluconazol 200 mg/daily.

Figure 1 Brain MRI revealed a single right, large cortico-subcortical temporo-parieto-occipital area of demyelination, hypointense in T1 with perilesional edema and mass effect (arrow).

Figure 2 Axial MRI brain scan shows the lesion hyperintense in FLAIR, with mass effect on the middle line structures and collapse of the occipital ipsilateral ventricular prolongation (arrow).

Figure 3 Histopathological examination of stereotactic brain biopsy revealed oligodendrocytes with large intranuclear inclusions and large, "bizarre" astrocytes with hyperchromatic nuclei, named reactive astrocytes. These findings were consistent with a diagnosis of progressive multifocal leukoencephalopathy.

Figure 4 Axial MRI brain scan post-treatment showing a right sequela cortico-subcortical parieto-occipital image, hypointense in T1 compatible with a minimal sequela gliosis (arrow)

Figure 5 MRI brain scan after treatment shows a resolution of the described lesion.

On physical examination he was afebrile, fully conscious and oriented with left hemiparesis and headache and signs of intracranial hypertension. The remaining physical examination was normal. A CD4 T cell count was 126 cell/ μ L. Brain MRI revealed a single right, large cortico-subcortical temporo-parieto-occipital area of demyelination, hypointense in T1 and hyperintense in T2-weighted and FLAIR, with perilesional edema and mass effect on the middle line structures and contrast enhancement (Figures 1 and 2). Antitoxoplasma gondii therapy was started without clinical response after two weeks. At this time, a stereotactic brain biopsy was performed; histopathological examination revealed multifocal and microscopic foci of demyelination, hyperchromatic, enlarged oligodendroglial nuclei containing abnormal inclusions and enlarged bizarre astrocytes with lobulated and hyperchromatic nuclei (Figure 3). These findings were consistent with a diagnosis of PML. Detection of JCV in biopsy smears was negative by polymerase chain reaction (PCR). The patient was started on the same scheme of ART plus corticosteroids, prednisone 60 mg in two divided doses per day with a rapid improvement. After two years of follow-up, the patient is still in a good clinical condition. His last CD4 T cell count was 352 cell/ μ L and the plasma viral load was undetectable. The last MRI scan of the brain showed a right sequelar cortico-subcortical parieto-occipital image, hypointense in T1, hyperintense in T2 and hypointense in FLAIR, consistent with gliosis. This lesion is associated with a mild to moderate retraction of the brain ventricular system (Figures 4 and 5).

Discussion

Progressive multifocal leukoencephalopathy (PML) is a CNS infection caused by the polyomavirus JC that compromises the oligodendrocytes and the myelin protein. Generally, this condition is strongly associated with HIV-1 infection and in rare cases with other conditions characterized by a compromised immune response. Most recently, PML has been described in association with the use of humanized monoclonal antibodies^{5,6}. PCR studies demonstrate JCV-DNA in the brains of patients without PML, especially in oligodendrocytes and astrocytes^{6,7}. The frequency of PML in HIV-1 infected patients varies from 0.7% to 9.8%, but a neuropathological autopsy series of Thurhner et al.³ reported the highest prevalence highest (11%).

The most common clinical manifestations of PML include weakness (80%), neuro-ophthalmological alterations such as disturbances of visual field (50%) and cognitive deterioration.

Neuropathology examination reveals multiple areas of demyelization varying in size and grade. All CNS regions can be involved, but the lesions are predominant in the parieto-occipital lobes. Cerebellar, brainstem and spinal cord involvement is less frequent⁴.

In the classic form of the disease, PML shows little or no inflammation. MRI showed no contrast enhancement and no mass effect⁸. By contrast, neuroimaging findings of inflammatory forms of the disease include the presence of contrast enhancement, perilesional edema and mass effect on the middle line structures, as we saw in our patient^{2,9,10}. The presence of enhancement and mass effect in PML lesions, as in our patient, is infrequent and is seen in long-term survival patients associated with ART¹⁰⁻¹². MRI spectroscopy shows a high concentration of choline (Cho), a decreased peak of N-acetyl-aspartate (NAA) and variable myoinositol levels. The presence of lactate and lipids, indicating necrosis or tissue anaerobiosis, can be detected in many patients¹⁰.

PML might develop in HIV+ patients shortly after the initiation of ART as a form of IRIS⁷. In a retrospective analysis of 39 patients with PML, five (13%) presented an inflammatory form of the disease. Specific cytotoxic T lymphocytes for JCV were detectable in four patients and the outcome was favorable in three of them⁶.

Diagnosis of PML includes the detection of JCV-DNA in cerebrospinal fluid (CSF) by PCR. In HIV-1 infected patients without ART, the sensitivity ranged from 72% to 92% and the specificity from 92% to 100%. In the appropriate clinical context a positive result confirms the diagnosis¹³. When the detection of JCV-DNA in CSF is negative or when the neuroimaging findings contraindicate lumbar puncture as in our patient, stereotactic brain biopsy is needed to establish the diagnosis.

Relevant histopathological findings include the presence of large oligodendrocytes with typical virus-bearing nuclear inclusions and atypical giant astrocytes. Necrotic areas can also be found in the central foci³.

The definitive diagnosis of PML includes clinical and MRI findings and the study of CSF with evidence of VJC DNA. In atypical cases, the definitive diagnosis should be confirmed only by the biopsy smears, as in our patient.

Cinque et al.¹⁴ proposed a classification for HIV-1-associated PML based on the presence of inflammatory features. As a result, patients can be classified in the classic or non-inflammatory form of the disease and inflammatory PML. In the classic form there is no indication for corticosteroids, whereas in the inflammatory group, the initiation of corticosteroids should be considered with ART. We think that our patient should be included in the second form or inflammatory PML.

In a recent review of 12 patients treated with steroids, early and prolonged treatment was

associated with a better outcome³. Published data indicate that inflammatory responses in PML are not infrequent and they are generally associated with a favorable prognosis, as in our patient.

In conclusion, the knowledge of typical and atypical images of PML is important to differentiate this entity from other opportunistic infections and tumors that can involve the brain of HIV seropositive patients. Hence, infectologists, neurologists, radiologists and clinicians should not rule out the diagnosis of PML in the presence of atypical neuroradiological findings.

References

- 1 Äström KE, Mancall EL, Ricahrdson EPJr. Progressive multifocal leukoencephalopathy: hitherto unrecognized complication of chronic lymphatic leukemia and Hodgkin's disease. *Brain*. 1958; 81: 93-111.
- 2 Manzardo C, Del Mar Ortega M, Sued O, et al. Central nervous system opportunistic infections in developed countries in the highly active antiretroviral therapy era. *J Neurovirol*. 2005; 11: 72-82.
- 3 Thurnher MM, Post MJ, Rieger A, et al. Initial and follow up MR imaging findings in AIDS-related progressive multifocal leukoencephalopathy treated with highly active antiretroviral therapy. *Am J Neuroradiol*. 2001; 45: 977-984.
- 4 Perez-Liz G, Del Valle L, Gentilella A, et al. Detection of JC virus DNA fragments but not proteins in normal brain tissue. *Ann Neurol*. 2003; 64: 379-387.
- 5 Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS related progressive multifocal leukoencephalopathy in the era of protease inhibitors. *AIDS*. 1999; 13: 1881-1887.
- 6 Du Pasquier RA, Korálnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol*. 2003; 9 (Suppl. 1): 25-31.
- 7 Tan K, Roda R, Ostrow L, et al. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology*. 2009; 72: 1458-1464.
- 8 Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antirretroviral therapy. *AIDS*. 2001; 15: 1900-1902.
- 9 Carson KR, Focosi D, Major EO, et al. Mononuclear antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab and efalizumab: a review from the research of adverse drugs events and reports (RADAR) project. *Lancet Oncology*. 2009; 10: 816-824.
- 10 Shah R, Bag AK, Chapman PR, et al. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol*. 2010; 65: 431-439.
- 11 De Luca A, Giancolla ML, Cingolani A, et al. Clinical and virological monitoring during treatment with intrathecal cytarabine in patients with AIDS-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 1999; 28: 624-628.
- 12 Krupp LB, Lipton RB, Swerdlow ML, et al. Progressive multifocal leukoencephalopathy: clinical and radiographic features. *Ann Neurol*. 1985; 17: 344-349.
- 13 Cinque P, Scarpellini P, Vago L, et al. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. 1997; 11: 1-17.
- 14 Cinque P, Korálnik IJ, Gerevini S, et al. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet*. 2009; 9: 625-636.

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