Progressive multifocal leukoencephalopathy: four cases of JCV infection in iatrogenic immunocompromised patients

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Introduction and Purpose

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system (CNS) caused by John Cunningham Virus (JCV). The disease occurs almost exclusively in immunocompromised individuals due to virus reactivation and the related cytolytic destruction of glial cells in the white matter, which results in sparse, asymmetric lesions of demyelination that progressively widen and coalesce. Clinical, radiological, and laboratory findings, including magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and/or biopsy with polymerase chain reaction (PCR) amplification for JCV DNA, are necessary to establish the diagnosis of PML. No specific treatments are still available.

In the last years, an increasing diffusion of **immunosuppressive treatments** and **transplantation procedures** has been registered and a growth in non-HIV-related PML frequency has been observed.

We reported **four cases of PML** who were admitted at our Neurological Clinic. None of the patients presented HIV-related immunodeficiency, all the cases were characterized by **iatrogenic immunosuppression** due to different treatments.

The aim of this case report review was **to define clinical, radiological, and laboratory characteristics of PML in four patients treated with different therapies**.

Figure 1. Patient M.D. MRI on DWI; at 1 month the border of diffusion restriction on DWI enlarged.

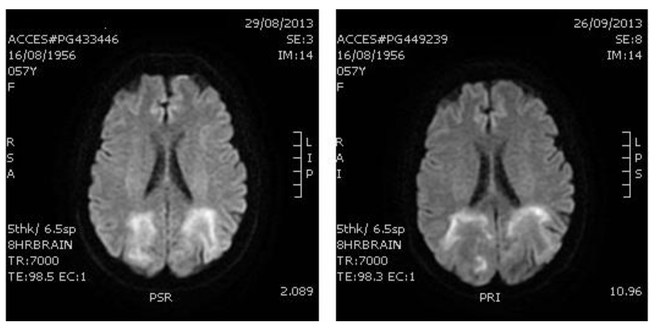


Figure 2. Patient R. C. MRI on DWI and T2-weighted; at 1 month the area of diffusion restriction on DWI moved laterally and the corpus callosum lesion became inactive.

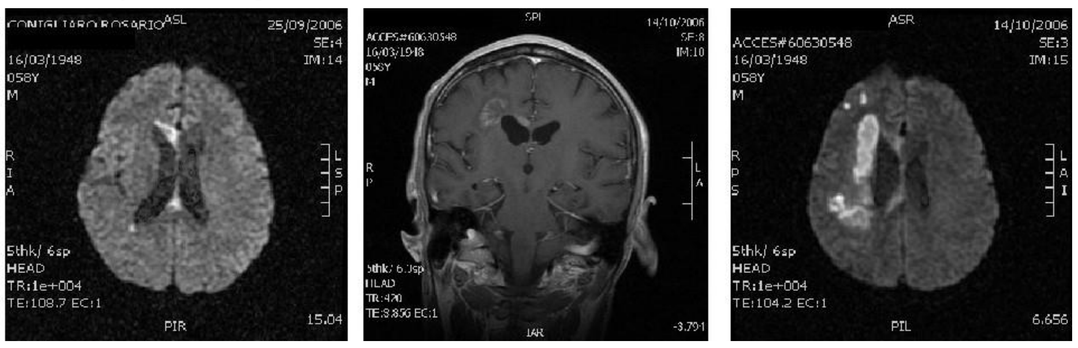
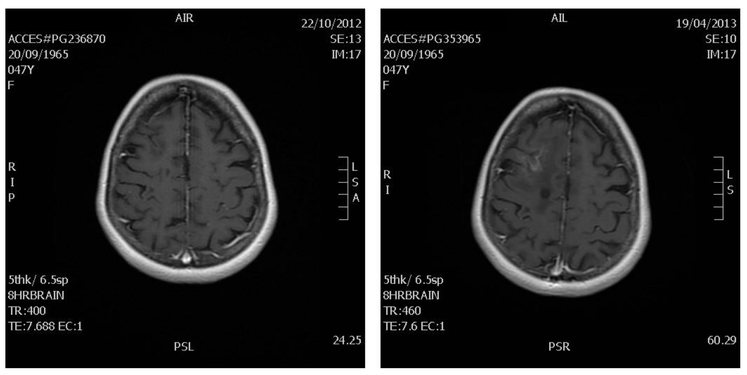


Figure 3. Patient F.C. MRI T1-weighted; control MRI at 1 month showed slight ring contrast enhancement.



Patients and Methods

We report **four cases of PML in immunocompromised patients**, respectively treated with (1) Natalizumab, (2) CHOP and Rituximab, (3) autologous stem cell transplantation and chemo-radiotherapy, and (4) Tacrolimus. All patients underwent neurological examination, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), JCV-DNA research on biological samples, and lymphocytes subpopulation study.

Results

Clinically, all described cases presented with motor, behavioral and cognitive disorders at **disease onset**. Cortical blindness, sensitive deficits, limb and gait ataxia, diplopia, and language disorders developed during **the first phases** of the disease and gradually worsened secondary to the enlargement of the lesions.

MRI revealed in all patients widespread progressive lesions, characterized by a prominent decreased signal on T1-weighted images and patchy increased signal on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences. The active margins showed diffusion restriction on diffusion-weighted sequences (DWI) (*figure 1* and *figure 2*). At follow-up, a progressive enlargement of the lesions were detected and three patients presented contrast enhancement at borders (*figure 3*), considered atypical in PML lesions. One patient developed inflammatory reconstitution syndrome (IRIS). On **MRS**, all cases presented a decrease in N-acetyl-aspartate (NA), which in three cases was associated with a peak of choline (Cho) (*figure 4*). MRS data completely consistent with those previously reported.

In one patient high-titer **JCV-DNA** was detected on plasma and urine, while **CSF analysis** confirmed JCV colonization in two patients. The fourth patient had low-titer JCV-DNA on **blood and brain biopsy** showed a pattern of subacute necrosis (*table 1*). **Lymphocyte subpopulations** showed a normal pattern in two patients; the other two patients presented low percentage of B-cells and an expansion of cytotoxic T-cells; in addition, one of them presented a decrease of T-helper cells (*table 1*).

Two patients had already suspended **immunosuppressive therapy** at disease onset and in te other two it was suspended at diagnosis. Three patients underwent therapy with **Mirtazapine**, one of whom was treated with **Mefloquine** in add-on. No improvement was observed at clinical evaluations.

Table 1. Patient laboratory data: (left) JCV-DNA on biological samples and (right) lymphocytes subpopulations

Patient	JCV-DNA	Cerebral biopsy
F. C.	positive on CSF	not performed
F. M.	positive on CSF	not performed
M. D.	positive on plasma and urine	not performed
R. C.	negative	subacute necrotising process without lympho-monocytic infiltrates

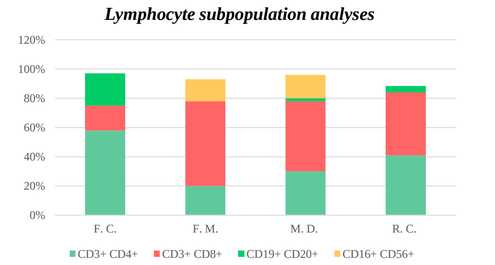
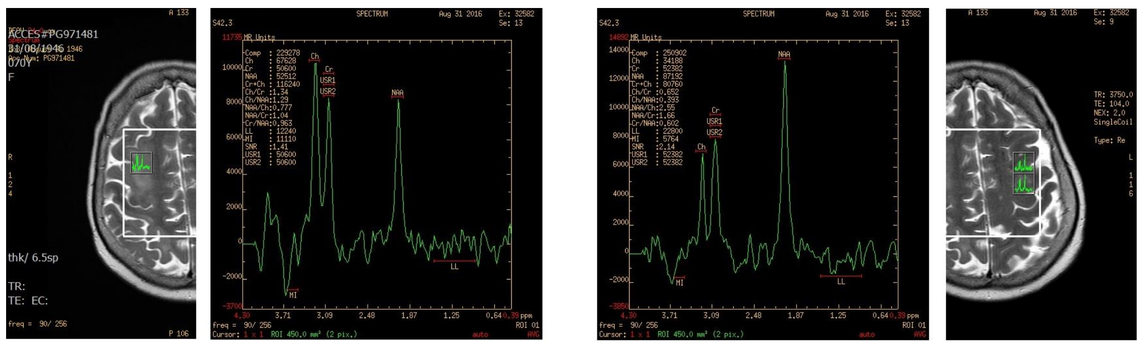


Figure 4. Patient F.M. MRS on lesion (left) and normal tissue (right). In the involved area an inversion of Cho and NA is registered.



Discussion

Clinical onset, MRI and MRS was highly suggestive of PML in all patients, despite three of them presented contrast enhancement, rarely observed. To confirm the diagnosis, **JCV-DNA research** was conducted in all patients. In three cases high-titer JCV-DNA was detected on biological sample. Conversely, in one patient biological sample and brain biopsy failed to clearly detect JCV-DNA, despite MRI was highly suggestive of PML. **Lymphocyte subpopulation analysis** did not reveal a common pattern. Notwithstanding the anecdotal evidence of efficacy of Mefloquine and Mirtazapine, **no significant clinical improvement** was observed in our clinical records and a progressive worsening of neurological status was registered.

References:

1. Hou J, Major EO – Progressive Multifocal Leukoencephalopathy: JC Virus Induced Demyelination in the Immune Compromised Host. Journal of Neurovirology 2000; 6 (Suppl 2): S98-S100
2. Koralnik IJ – Progressive Multifocal Leukoencephalopathy Revisited : Has the Disease Outgrown Its Name?. Annals of Neurology 2006; 60: 162-173
3. Shah R, Bag AK, Chapman PR, Cure JK – Imaging Manifestations of Progressive Multifocal Leukoencephalopathy. Clinical Radiology 2010; 65: 431-439

Conclusion

- **We reported four cases of PML in iatrogenic immunocompromised patients with a typical clinical presentation. Nonetheless, diagnostic findings were not completely consistent with classical PML.**
- **These findings consist with the importance not to exclude the diagnosis in presence of atypical characteristics of disease when anamnestic and clinical data are highly suggestive of PML.**
- **Concluding, several conditions could fail the diagnosis of PML, but considering the increasing risk due to the widening diffusion of biological immunosuppressive therapies and stem cell transplantation, more studies should be conducted to improve the diagnostic and therapeutic management of patients.**