Progressive multifocal leukoencephalopathy in a patient with chronic lymphocytic leukemia treated with Rituximab

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Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system, which affects the white matter. It is caused by reactivation of latent John Cunningham virus (JCV) in the context of immune system suppression, particularly in patients infected with human immunodeficiency virus (HIV) and in transplantation recipients, although it was first described in patients with chronic lymphocytic leukemia (CLL) and Hodgkin lymphoma. The increasing number of PML cases recently diagnosed under monoclonal antibody therapy (Rituximab, Alemtuzumab, Brentuximab and Natalizumab) highlights the role of the immune system suppression in the pathogenesis of PML. Rituximab is a CD20-specific monoclonal antibody that is effective in treating CLL. Rituximab therapy has been associated with reactivation of viral infections such as hepatitis B, cytomegalovirus, herpes simplex virus (HSV), varicella zoster virus (VZV), West Nile virus and JCV (1). The pathophysiology of rituximab-associated PML is unclear; some findings suggest that hematopoietic progenitor cells may be a site of viral latency. Hematopoietic progenitor cells mobilized into the peripheral blood during chemotherapy may have been infected with latent JCV and may have facilitated the hematogenous spread of JCV into the central nervous system (CNS) (2).

*We report the case of a 78-year-old Caucasian male patient with CLL, who was treated with Bendamustina and Rituximab. He had a history of atrial fibrillation in therapy with oral anticoagulant. He was subjected to a total of six infusions of chemotherapy, then about 15 days after the last dose of Rituximab he presented a mild right-sided hemiparesis and cognitive alterations. This symptomatology was initially interpreted as a stroke event but the head CT scan performed in the Emergency Room showed vasogenic edema in the right superior frontal cortex. The INR value was out of the therapeutic range. An MRI of the brain showed a hyperintensity on T2-weighted images in the white matter involving the right frontal subcortical region without contrast enhancement; there was no mass effect, hemorrhagic or ischemic lesions **(Figure 1 A)**. Blood count measurements showed a total white cell count of 4,6×103/L. Flow cytometry of the peripheral blood lymphocytes revealed a non-clonal cell population; CD4+ and CD8+ counts were 28 cells/μL (normal limits, 700–1100 cells/μL) and 107 cells/μL (normal limits, 500-900 cells/μL), respectively. Serology for HIV, HBV, HCV, HSV and Toxoplasma was negative. Cerebrospinal fluid (CSF) analysis indicated a normal cell count, and normal protein and glucose levels, with no evidence of neoplastic cells. Polymerase chain reaction (PCR) analysis of the CSF was negative for HSV RNA, CMV RNA, and VZV DNA and positive for JCV DNA. According to the presence of classic radiographic findings and clinical features coupled with a positive CSF JCV PCR, a diagnosis of PML was made **(Figure 2)** (3).*
*Treatment with mirtazapine (30 mg/day) was initiated. On follow-up MRI, performed 2 weeks later, the T2 lesion was further enlarging, with still no increase of signal after gadolinium **(Figure 1 B)**. Rapid clinical progression correlated to further worsening on MRI. After one month from the onset of the neurological symptoms, the patient died.*

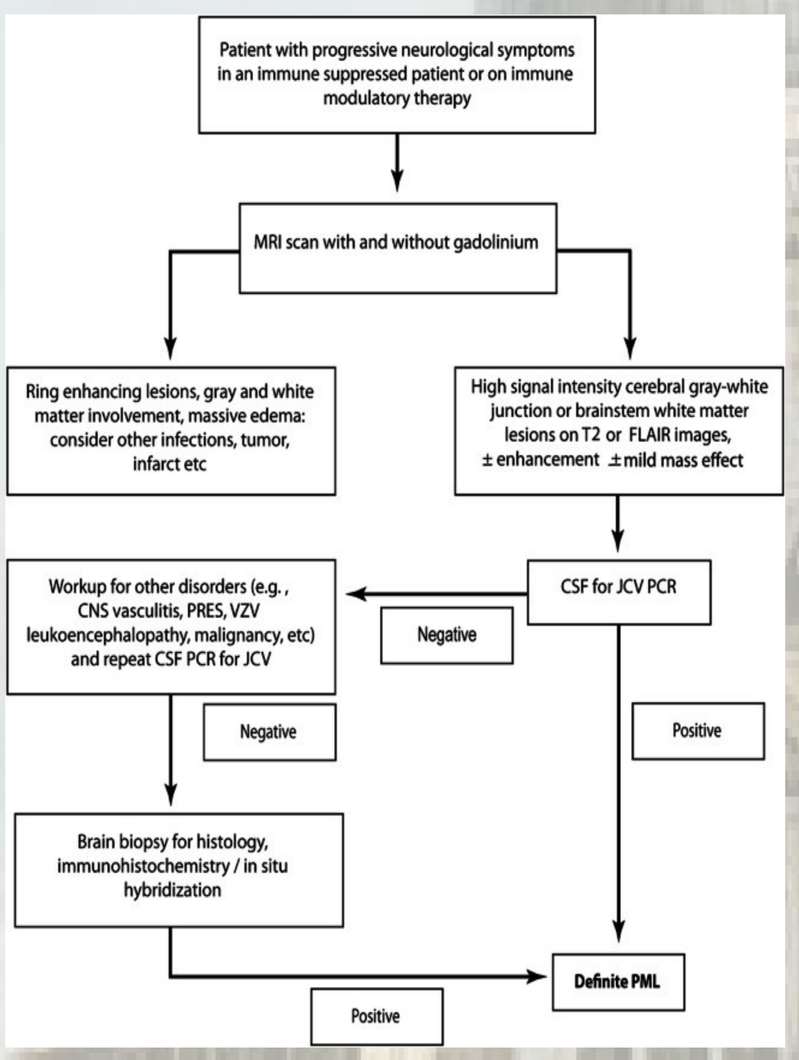
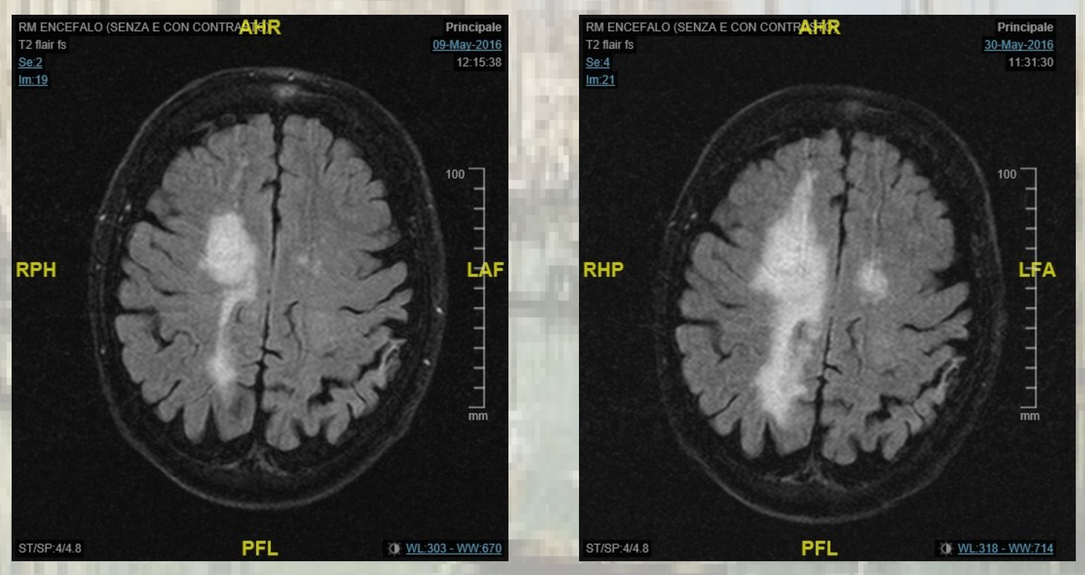


Figure 2

Algorithm for diagnosing progressive multifocal leukoencephalopathy (3).



A ***B***

Figure 1
Fluid-attenuated inversion recovery (FLAIR) images in the affected regions. A: hyperintensity in the white matter involving the right frontal subcortical region B: Increment in the extension and intensity of the lesion 2 weeks later the diagnosis.

Bibliography:

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2.Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the research on adverse drug events and reports project. Blood. 2009;113:4834–40.
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Risk factors for developing PML in HIV-infected people include low CD4+ lymphocyte count, whereas those in HIV-negative people remains a matter of debate (2). In our patient, PML was associated with immunological dysfunction in relation to the baseline hematological disease, receiving previous treatments (Bendamustina) and monoclonal antibody therapy with Rituximab. All these elements, individually or in combination, led to an immunosuppression, maintaining a low CD4+ count (28 cells/μL). The most common symptoms in PML related to rituximab use are confusion, hemiparesis, incoordination, speech disturbance and visual problems. There is no distinct treatment for this condition. The monoclonal antibody agents can remain in the body for many months after treatment has stopped; therefore, plasma exchange is used to remove remaining drug from the system. Mirtazapine has been used due to its serotonin receptor blockade properties with variable results. Mefloquine has been found to have anti-JCV activity; however, its efficacy has yet to be determined. The outcome of patients with PML is mostly unfavorable, leading to death in 90% with median survival of only two months.
In conclusion, Rituximab administration may increase risks of developing PML, although the absolute risk of developing PML is probably low. As use of Rituximab expands to diverse clinical settings, clinicians and patients should be aware of the potential for PML after rituximab therapy. Early diagnosis before irreversible neurologic damage has occurred will be crucial for evaluation of the efficacy of new antiviral treatments.

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