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► To cite this version:

Carlo Visco, Enrico Marchioni, Fabrizio Pomponi, Pasquale Ferrante, Serena Delbue, et al.. Progressive multifocal leuconcephalopathy and autoimmune haemolytic anemia in chronic lymphocytic leukaemia: more than a fortuitous combination?. *Annals of Hematology*, 2008, 88 (2), pp.189-191. 10.1007/s00277-008-0567-8 . hal-00486522

HAL Id: hal-00486522

<https://hal.science/hal-00486522v1>

Submitted on 26 May 2010

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Progressive multifocal leucoencephalopathy and autoimmune haemolytic anemia in chronic lymphocytic leukaemia: more than a fortuitous combination?

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Received: 25 April 2008 / Accepted: 17 July 2008 / Published online: 12 August 2008
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Dear Editor,

Progressive multifocal leucoencephalopathy (PML) is a subacute demyelinating disorder of the central nervous system usually affecting immunocompromised individuals [1], caused by JC polyomavirus (JCV) reactivation. Apart from being a relevant cause of morbidity in human immunodeficiency virus-seropositive (HIV+) patients, PML may be observed during lymphoproliferative disorders, rheumatic disease or bone marrow transplantation. The JCV remains lifelong latent in the kidneys and in the

peripheral blood mononuclear cells (PBMC) [2] of infected patients unless immunosuppression occurs, allowing infected PBMC to migrate to the brain, where astrocytes and oligodendrocytes support JCV replication resulting in neurologic damage [3]. Normal T-cell lymphocytes seem to play a crucial role in this setting, preventing proliferation and migration of infected PBMC. Low numbers of CD4+ T-lymphocytes have been related to PML development, while functional specific CD8+ T-cells are involved in early control of PML [4]. Thus, immunosuppressive and immunomodulating treatments may enhance the risk for reactivation of latent JCV. This is the case of natalizumab, a humanised monoclonal antibody directed against $\alpha 4$ integrins, which has been associated to PML occurrence in patients treated for multiple sclerosis and Crohn's disease [5]. Rituximab, a monoclonal antibody against B-cell lymphocytes, and fludarabine, a purine analogue that impairs the function of both T- and B-lymphocytes, have been associated with the occurrence of PML in haematologic malignancies and rheumatic disease [6], but a causal relation between these drugs and PML seems yet speculative.

We report a case of a 63-year-old HIV-negative male patient with a 10-year history of chronic lymphocytic leukaemia (CLL). Assessment of prognostic variables at presentation revealed a mutated pattern with VH3-21 gene usage and low expression of Zap-70 and CD38 by tumor cells, with a 13q deletion. The patient had been previously treated with two courses of chlorambucil and two courses of fludarabine-based chemotherapy. One month after the last chemotherapy, while the patient was still rituximab naïve, he presented to our Department because of an

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isolated progressively worsening visual loss. Anamnesis revealed a recent episode of transient diplopia. Brain computed tomography and magnetic resonance imaging (MRI) revealed aspecific non-enhancing bilateral occipital lesions. Cerebrospinal fluid (CSF) cell count and biochemical analysis was within normal limits. Haematologic assessment showed increasing lymphocytosis (from 130 to $170 \times 10^3/\mu\text{L}$), accompanied by a deep fall in the haemoglobin level (from 12.4 to 6.7 g/dL) and by swelling of the spleen and lymphadenopathies. Serum immunoglobulin levels were low (IgG 513 mg/dL; IgA 10 mg/dL; IgM 11 mg/dL), and immunophenotypic analysis revealed a striking reduction of CD4+, and CD8+ T-lymphocytes on peripheral blood (0.2 and $0.05 \times 10^3/\mu\text{L}$, respectively). A Coomb's positive autoimmune haemolytic anemia (AHA) by IgG warm antibodies was diagnosed. The patient was then started with a regimen including rituximab, cyclophosphamide, vincristine and prednisone (R-COP), completing three cycles and obtaining a rapid and complete regression of lymphadenopathies, splenomegaly, lymphocytosis, and of the AHA. The visual defect remained stable during the 2 months of immunotherapy. However, 2 months after the end of treatment, the patient was hospitalised because of acute dyspnoea and persistent fever. Cytomegalovirus reactivation was detected and therapy with intra-venous gancyclovir and antibiotics was started, with improvement of respiratory symptoms. A new MRI of the brain showed bilateral non-enhancing foci of white matter abnormalities in the occipital regions, compatible with a diagnosis of PML. Biochemical analysis and cell count of the CSF was within normal limits, but JCV search was positive in both blood and CSF by real time PCR (3.58×10^4 copies/mL and 1×10^8 copies/mL, respectively). Cidofovir therapy was started, but neurologic symptoms progressed to hemiparesis, and then to a cognitive impairment in 1 month. The patient died 3 months later.

Visual loss, together with motor weakness, is the most frequent initial deficit in patients affected by PML. To the best of our knowledge, this is the first report describing the concomitant occurrence of neurologic symptoms attributable to PML and AHA in a patient with CLL. However, this association seems not surprising. CLL is typically characterised by profound immunosuppression, since primary antibody response declines early during the disease. Furthermore, T-cell response is impaired by pathological regulatory cytokines and by interactions between normal T- and B-lymphocytes and CLL B-cells. In this setting, the altered function of regulatory T-cells (CD4+CD25+FOXP3+), which are also hampered by immunosuppressive treatments, allows the emergence of normally suppressed B-cell clones producing autoantibodies, giving rise to autoimmune phenomena. AHA is the most frequent autoimmune complication in the course of CLL, and its frequency significantly increases in heavily pre-treated patients with progressive disease, espe-

cially after fludarabine monotherapy [7, 8]. Only about 2% of patients with CLL develop haemolysis after one line of therapy, compared with about 5% of patients who have received more than one previous treatment and 20% of heavily treated patients [9]. Reduction of T-cell count, hypogammaglobulinemia and the immunosuppressive effect of treatment represent the pathogenetic link between occurrence of AHA and infectious complications as PML. As outlined before, at onset of neurologic symptoms, both CD4+, and CD8+ T-cell count and immunoglobulin levels were strikingly reduced in our patient and never recovered during the subsequent controls.

Although many cases of PML have been reported outside the HIV epidemic in patients with CLL treated with fludarabine [10], current and new immunosuppressive treatments may increase the risk of reactivation of latent infections. In our patient, neurologic symptoms preceded administration of rituximab, then remained stable for several months after the first dose, but worsened thereafter. Thus, while a causal role for this drug in the development of PML seems not likely in our patient, immunotherapy may have contributed to the subsequent progression to hemiparesis and cognitive impairment. Our case shows that PML must be considered in patients experiencing acute onset of neurologic symptoms in the CLL setting, especially when heavily pre-treated with agents impairing T-cell function like fludarabine.

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