JC papovavirus leukoencephalopathy after first line treatment with CHOP and rituximab

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Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating infection of the central nervous system caused by the JC papovavirus usually seen among immunocompromised patients. PML arises upon JC virus reactivation during periods of immunosuppression. PML may be seen among patients with lymphoproliferative disorders and immunosuppression induced by chemotherapy.[1] Recently, an association between PML and rituximab in the setting of autologous[2, 3] or allogeneic[4] transplantation has been suggested.

We report the first case of a woman with a non Hodgkin lymphoma (NHL) who developed PML after a combination of rituximab with chemotherapy as first line treatment.

A 67-year-old woman suffered from a mantle cell lymphoma diagnosed on splenomegaly and hyperlymphocytosis. Staging showed a stage IV with bone marrow involvement. The patient was treated with a combination of rituximab (375 mg/m^2) and chemotherapy with standard CHOP: cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristin 2 mg, and oral prednison 100 mg given in 3-week cycles. She received eight cycles of treatment. Evaluation after the eight cycles showed a complete remission. One month after the last chemotherapy, the patient rapidly presented psychiatric disturbances with speech dysfunction and paranoia delirium. PML was suspected on magnetic resonance imaging showing frontal and temporal leukoencephalopathy. JC viral DNA was detected in the cerebrospinal fluid. HIV serology was negative. Her total lymphocyte count was 470/∝L with 110/∝L CD4$^+$ and 310/∝L CD8$^+$. Peripheral B cells were decreased with 0/∝L CD19$^+$. Quantitative serum immunoglobulins were normal with an immunoglobulin (Ig) G of 7.77 g/L, IgA 1.95 g/L, and IgM 0.91 g/L. A treatment with cidofovir was started but cutaneous allergic reaction was noted after five doses. Neurological disturbances worsen progressively despite improvement of her immune status at four months (total lymphocyte count was 771/∝L with 421/∝L CD4$^+$ and 341/∝L CD8$^+$). Cerebral magnetic resonance imaging performed three months after the diagnosis showed an increase of the leukoencephalopathy lesions. The patient deceased six months after the beginning of symptoms.

Rare cases of PML have been reported among patients with lymphoma. A recent survey retrospectively analyzed 46 cases of PML occurring during lymphoproliferative diseases. 1 The implication of rituximab in these cases, without transplantation setting, has not been highlighted. Moreover, the patients reported were often in relapse, and were heavily pre treated.[1]

Four cases of PML were recently described in patients who were treated with chemotherapy, transplantation (autologous for three and allogeneic for one) and peritransplantation rituximab.[2-4] Despite these cases, a direct association between rituximab and PML remains moreover speculative. The addition of peritransplantation rituximab which results in delayed T-cell reconstitution after transplantation may be involved in the occurrence for late infectious diseases.

In our case, the link between rituximab treatment and PML development appears disputable, mostly because the patient showed at the same time a severe suppression of T cell immunity (110 CD4$^+$ T cells/∝L). Interestingly, another case of PML was recently reported in a patient treated with rituximab without transplantation.[5] The patient was 62 year-old with chronic lymphocytic leukemia for 14 years and Richter transformation for 2. He was heavily pre treated (chlorambucil, fludarabine) although PML developed 14 months after 6 courses of rituximab with chemotherapy.

Our patient is, to our knowledge, the first case of PML after a combination of CHOP with rituximab, in first induction procedure. Although the contributory role of rituximab remains speculative, our additional case highlights the need for an accurate surveillance, even in patients not heavily pre treated, as in first induction procedure with CHOP and rituximab.

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