Remission of severe antiphospholipid syndrome associated with non-Hodgkinís B-cell lymphoma after combined treatment with rituximab and chemotherapy

The association of lymphoid neoplasms and antiphospolipid antibodies (APA), with or without thromboembolic complications, has been reported in several cases. We describe one case of B-cell non-Hodgkinís lymphoma (NHL) in which the combination of rituximab with standard chemotherapy led to the complete remission of a severe hypercoagulable state associated with APA.

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Antiphospholipid syndrome (APS) is a disorder characterized by a hypercoagulable state due to autoantibodies that recognize phospholipid complexes. Antiphospholipid antibodies (APA) are a heterogeneous group of type G, M or A immunoglobulins reacting with negatively charged phospholipids. The most frequently detected APA are lupus anticoagulant (LA) antibodies, anticardiolipin antibodies (ACLA) and anti β2 glycoprotein I antibodies.[1,2] The presence of APA in the plasma promotes a prolongation of phospholipid-dependent coagulation times, primarily the activated partial thromboplastin time (aPTT). In a significant proportion of cases APS develops in otherwise healthy individuals, while in other cases it can be associated with autoimmune diseases, particularly systemic lupus erythematosus, or neoplasms, mostly of lymphoid origin.[3-7] The rate of thrombosis in patients with APA associated with lymphoid neoplasms who were treated with conventional chemotherapy was reported to be higher than that in controls.[8] Treatment for APA consists in the therapy of associated autoimmune diseases or thrombotic events.3 Some authors have described the efficacy of rituximab, a monoclonal humanized anti-CD20 antibody capable of producing B-cell depletion, used in combination with chemotherapy in the treatment of CD20 positive B-cell lymphomas,[9] and in inducing remission from a life-threatening hypercoagulable state associated with APA in one case of systemic lupus erithematosus.[10]

We report here the case of remission of a severe hypercoagulable state in a patient with APS who received chemotherapy combined with rituximab for the treatment of non-Hodgkin's B-cell lymphoma.

In June 2002, a 53-year old man was urgently admitted to hospital because of massive deep bilateral venous thrombosis of the femoral veins and pulmonary embolism. Treatment with continuous intravenous heparin infusion was started immediately. The clinical examination detected considerable enlargement of the spleen and abdominal ultrasonography also revealed lymphoadenopathy. Thereafter the patient was referred to our Hematology Institution. A bone marrow trephine biopsy demonstrated that he had marginal zone non-Hodgkin's B-cell lymphoma. In the meantime, a diagnosis of APS was made according to the *Sapporo criteria* (see Table 1).[1] The patient had recurrent venous thrombosis in all four limbs in spite of continuous intravenous heparin infusion, and the aPTT being maintained about 2.5 times the mean of the normal range. The first cycle of chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) was partially effective on the lymphoma, but did not modify APA titers. The three subsequent cycles were administered in association with rituximab 375 mg/sqm (R-CHOP); complete regression of lymphoadenopathy and bone marrow involvement was documented after this treatment.

Table 1. Response to rituximab in a case of antiphospholipid antibodies associated with non-Hodgkin's B-cell lymphoma.

Parameter	*Diagnosis*	*After R-CT*
aPTT (ratio)	1.96	1.06
dRVVT (ratio)	1.67	1.15
dRVVT-ICA (%)	33	1
dRVVT-CT	positive	negative
aPTT-LA (ratio)	1.79	1.11
aPTT-LA ICA (%)	75	11
Staclot-LA	positive	negative
ACA IgG (U/mL)	109	1.8
ACA IgM (U/mL)	6.7	5.1

R-CT, rituximab-chemotherapy; aPTT, activated partial thromboplastin time; dRVVT, dilute Russel viper venom time; ICA, index circulating anticoagulant; CT, confirmatory test; LA, lupus anticoagulant; ACA, anticardiolipin antibodies. Normal ranges: aPTT (ratio), 0.8-1.15; dRVVT (ratio), < 1.20; dRVVT ICA, < 15%; dRVVT-CT, negative; aPTT-LA (ratio), < 1.20; aPTT-LA ICA, < 15%; Staclot-LA, negative; ACA-IgG and ACA-IgM, < 20 U/mL.

The APA titers progressively decreased until becoming normal and the patient had no other thrombotic events after the first administration of R-CHOP. In December 2002, splenectomy was performed given the persistence of the spleen enlargement. The histologic findings were negative for lymphoma involvement. After discharge the patient started life-long anticoagulation with warfarin. At the time of writing, neither progression of lymphoma nor an increase of APA titers has been documented. Our observation extends previous findings on the efficacy of rituximab in inducing remission from the severe hypercoagulable state associated with APA also to one case of non-Hodgkin's B-cell lymphoma. In fact, after adding rituximab to chemotherapy, no new thrombotic episodes were observed in this patient who had suffered recurrent massive thromboses in all four limbs and pulmonary embolism, which progressed despite continuous intravenous heparin infusion and conventional chemotherapy treatment. In conclusion, we believe that including rituximab in the treatment of B-cell lymphomas with associated APS might be advisable.

Dino Veneri,[1] Achille Ambrosetti,[1] Massimo Franchini,[2] Federico Mosna,[1] Giovanni Poli,[3] Giovanni Pizzolo[1]

[1]Dipartimento di Medicina Clinica e Sperimentale, Sezione di Ematologia, Università di Verona, Verona; [2]Servizio di Immunoematologia e Trasfusione, Azienda Ospedaliera di Verona, Verona; [3]Dipartimento di Scienze Biomediche e Morfologiche, Università di Verona, Verona;

Correspondence: Dino Veneri, MD
Sezione di Ematologia Policlinico G.B. Rossi, Verona, Italy
E-mail: dino.veneri@univr.it

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