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Splenic marginal zone lymphoma with Evans' syndrome, autoimmunity, and peripheral gamma/delta T cells

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Dear Editor,

Several theories have tried to explain the occurrence of autoantibodies in lymphoid malignancies. Autoimmune phenomena like Evans' syndrome, lupus anticoagulants, autoimmune thrombocytopenia, and autoimmune hemolytic anemias are frequently associated with lymphomas [4, 5]. Recently, systemic lupus erythematosus (SLE) was associated with an increased risk of diffuse large B cell and marginal zone lymphomas [3]. Splenic marginal zone lymphoma (SMZL) is an indolent B cell lymphoma, which generally presents splenomegaly and involvement of both bone marrow and peripheral blood. In this report, we describe a patient with autoimmunity and bone marrow infiltration that probably broke the mechanisms of central tolerance in bone marrow producing the emergency of new auto-reactive clones and autoantibodies.

A 60-year-old man had a 12-month history of B symptoms. Physical examination was unremarkable, except for the presence of massive splenomegaly. A computerized tomography (CT) scan of the abdomen confirmed spleno-

megaly and visualized enlarged lymph nodes in retroperitoneum (Fig. 1). Blood smear and peripheral blood immunophenotype suggest SMZL with villous lymphocytes.

The patient underwent laparotomy for splenectomy, lymph node, and bone marrow biopsies. Histology corresponds to SMZL. Follow-up studies detected the persistence of lymphoid neoplastic cells (1.4%) and a $\gamma\delta$ T cell population (TCR $\gamma\delta$ CD2+, CD3+, CD5 low+, CD7+, CD8 low+/-, CD16 -/+ CD56+, CD57 +/-) that represented 12% of the cells in peripheral blood. Five months after diagnosis, the patient presented with abdominal discomfort. On a CT scan, abdominal adenopathic progression was observed and the two populations (3.4% of SMZL and 4.9% of $\gamma\delta$ T cells) persisted in peripheral blood. The patient received eight cycles of chemotherapy with cyclophosphamide–doxorubicin–vincristin–prednisone regime, resulting in radiological remission. At this moment, flow cytometry of peripheral blood revealed 0.0026% of tumor cells and 13.75% of $\gamma\delta$ T cells.

Four months after chemotherapy, the patient was admitted to the hospital with a recurrence of SZML. He showed, besides, respiratory insufficiency and Evans' syndrome, associated with high titers of antiphospholipid antibodies, lupus anticoagulant and prolonged partial thromboplastin time, high levels of immune complexes, and low levels of both immunoglobulins and C3 and C4 fractions of complement. Antinuclear, antineutrophil cytoplasmic, anticardiolipin, antiplatelets, anti-HLA I, and anti-EPCR antibodies were also detected. CT scan ascertained the presence of pulmonary emphysema and hepatomegaly, without associated enlarged lymph nodes. Peripheral blood flow-cytometry indicated an increase in the neoplastic B cell population (50%) and a decrease of $\gamma\delta$ T cells (5%). The bone marrow biopsy confirmed lymphoid infiltration (SMZL 35% and $\gamma\delta$ T cells 4%) by immunophenotype.

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Fig. 1 Massive splenomegaly

With the diagnosis of SMZL relapse, chemotherapy with fludarabine–mitoxantrone–dexamethasone and rituximab (FMD-R) was started. Surprisingly, after one cycle of FMD-R, all the autoimmune tests became negative, C3 and C4 fractions of complement reached normal levels, and immune complexes were found to be negative. After three cycles, a complete remission was achieved. Flow-cytometry of peripheral blood did not detect any B cells, although the $\gamma\delta$ T cells persisted, representing 2.5% of all peripheral blood cells and 64% of the circulating lymphocytes.

It is generally accepted that most auto-reactive B cells are eliminated from the normal repertoire. Within the bone marrow, B cells that rearrange and express self-reactive receptors at the immature stage are either edited or eliminated by apoptosis. Defects in the retention of self-antigen could result in the loss of efficient negative selection and escape of self-reactive B cells to the periphery. Complement-binding in immune complexes or

in autoantigens could protect from autoimmunity by enhancing presentation of antigens to self-reactive B cells at the immature stage or in the T1–T2 transitional stage [1, 2]. Interestingly, marginal zone B cells have been shown to initiate immune responses by transporting IgM antigen-immune complexes into the follicle and may play an important role in the removal of senescent cells, apoptotic debris, and immune complexes. The fact that removal of the spleen appears to alter the disease distribution in some patients with SMZL, resulting in an increase in the bone marrow infiltration, could contribute towards the migration of neoplastic SMZL with immune-complexes and auto-antigens (e.g., apoptotic debris evoked by chemotherapy) to the bone marrow and alter central tolerance. Abnormally expanded $\gamma\delta$ T cells could provide increased amounts of help to B cells to produce autoantibodies. Importantly, several autoimmune diseases show an expansion of altered $\gamma\delta$ T cells like in Behcet's disease, rheumatoid arthritis, and SLE.

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