Autoimmunity in Chronic Lymphocytic Leukemia: Which B Lymphocyte is the Culprit?

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Chronic lymphocytic leukemia is a complex immunologic disorder originating from antigen-stimulated mature B lymphocytes [1]. Immune dysregulation is a hallmark of CLL and manifests itself in autoimmune diseases and stigmata that may occur before CLL is diagnosed, or, more frequently, in the course of the disease or its treatment [2].

CLL is the most common cause of autoimmune hemolytic anemia, although many other autoimmune manifestations have been described, such as thrombocytopenia, pure red cell aplasia, etc., usually occurring in the more advanced stages of CLL and among heavily pretreated patients. The frequency of autoimmune manifestations seems to be rising since the introduction of purine analogues in the treatment of CLL [3].

In a retrospective study published in this issue of *IMAJ* [4], Duek and co-workers report the characteristics of 115 CLL patients with autoimmune features from a cohort of 964 patients (12%) from the Registry of the Israeli Study Group on CLL. Most frequent immune manifestations included autoimmune hemolytic anemia (some fludarabine-related), isolated positive direct antiglobulin test, Hashimoto's thyroiditis, thrombocytopenia and Evan's syndrome. Interestingly, the presence of rheumatoid and antinuclear factors was also frequently found, confirming previous reports of ill-defined immune stigmata in CLL [5]. Decreased serum levels of complement components were measured in 15% of the CLL patients, a finding compatible with the possible role of a defective complement system in autoimmune manifestations in CLL [6].

The authors postulate that malignant B cells are the source of the autoantibodies, and as such, might disclose an activated phenotype pattern. They chose several laboratory parameters as evidence for a state of B lymphocyte activation and found that the B lymphocytes from CLL patients with autoimmunity are more frequently activated than among CLL patients without autoimmunity. The authors suggest that some degree of activation of B lymphocytes may be associated with the occurrence of autoimmune complication in B cell CLL. This conclusion, based on the expression of biological markers of malignant lymphocytes, does not imply that the leukemic B lymphocytes are actually producing the autoantibodies, but rather that they show their involvement in the antibody production. The involvement of the leukemic cell is essential to the development of the antibody. The CLL cell often secretes autoreactive immunoglobulin. In other studies, Broker et al. [7] stimulated CLL cells to secrete immunoglobulin M that reacted with a variety of autoantigens, while Sthoeger and co-workers [8] demonstrated the production of IgG autoantibodies by the CD5+B monoclonal CLL expressing surface IgG. Nevertheless, the antibodies produced by the CLL cells are usually IgM and are always monoclonal, while it has been established that anti-red blood cell autoantibodies found on the cells and in the sera in CLL are IgG of polyclonal origin. It is therefore the accepted current hypothesis that, in most cases, the autoantibodies are produced by residual normal cells and not by tumor cells.

CLL = chronic lymphocytic leukemia
Ig = immunoglubulin

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