Mixed cryoglobulinemia syndrome as an additional autoimmune disorder associated with risk for lymphoma development

We have read with great interest the article about autoimmune disorders and lymphoma subtypes by the InterLymph Consortium. We agree with the suggestion that local and chronic presentation of specific antigens may stimulate lymphocytes, progressing to host immune dysregulation and eventually resulting in the development of lymphoproliferative disorders and overt lymphomas. Numerous articles from our group and others support this hypothesis. Data suggest that the chronic antigen stimulus is most important in the initial phases of the illness, resulting in an increased number of highly proliferating cells. In such a cell population genetic errors can occur more frequently than normal and may explain why lymphoproliferation is sustained chronically even with removal of the antigen. The immunogenetic background of the host (the polymorphic HLA molecules) could favor reactivity to specific antigens and are found to be associated with autoimmune diseases.

Our letter calls attention to an additional autoimmune disorder with an increased risk for lymphoma development not mentioned by the authors, the mixed cryoglobulinemia (MC) syndrome, where the pathogenetic autoantibody is rheumatoid factor. This syndrome is of fundamental importance in the study of lymphomas linked to antigenic stimulation and autoimmunity. In fact, MC syndrome is the only autoimmune disease, besides celiac disease (CD), where a definite triggering antigen has been identified, that is, hepatitis C virus (HCV) in the former and gluten in the latter. In both CD and MC syndromes, there is a high risk of lymphoma development in organs that are chronically inflamed, liver and salivary glands for MC and small intestine for CD, respectively. Interestingly, the up-regulation of a growth factor required for B-cell proliferation, BLyS (B lymphocyte stimulator), has been shown by our group to be highly expressed in both MC and CD. In MC syndrome and associated indolent lymphomas the elimination of the viral infection may ameliorate disease and be accompanied by morphologic neoplastic regression in some cases. The biologic characteristics of MC syndrome are then of extreme importance for the study of the etiopathogenetic mechanisms linking antigen stimulation to autoimmunity and to lymphoproliferation.

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