HCV-POSITIVE MACROGLOBULINEMIA

Franco Dammacco, Domenico Sansonno Department of Internal Medicine and Clinical Oncology, University of Bari Medical School, Bari, Italy

Although an association between WM and HCV infection has been suggested as etiological in a few studies, subsequent and more accurate investigations failed to demonstrate such an association. However, a strikingly high prevalence of HCV infection has been definitely shown in mixed cryoglobulinemia with an IgM monoclonal component. Indeed, HCV infection plays a major role in these situations, leading to a massive clonal expansion of antigen-activated B-cells. An imbalanced distribution of expanded B-cell clones may be detected in different biologic compartments, suggesting that IgH VDJ mutational activities are differentially regulated. In HCV-positive IgM-related disorders B cell expanded clonotypes are mainly located in the liver and show highly diverse CDRH3 sequences, suggesting that they are the result of an antigen-driven response. A role for HCV in transforming IgM-expressing cells may be proposed, in that it directly interacts with B and T-cells through the receptor for the globular domain of C1q protein (gC1q-R). In type II cryoglobulinemic patients significantly higher levels of circulating gC1q-R have been found, which parallel specific mRNA expression in peripheral blood lymphocytes. gC1q-R circulates as a complexed form containing C1q and HCV core protein. In vitro studies have shown that release of soluble gC1q-R is regulated by HCV core-mediated inhibition of cell proliferation, indicating a deep dysregulation of cell cycle pathways. Notably, these findings seem relevant to the understanding of B-cell expansion in HCV-positive IgM-related disorders, in that B-cell receptors (BCR) specifically recognize both IgG Fc(345-355) and HCV-encoded protein(1238-2179) domains. This is consistent with the notion that BCR specificity is generated through a cross-reaction between a virus-associated immunodominant epitope and IgG autoantigen, thus contributing to the virus enrichment on the B-cell surface by the capture of the IgG/HCV-containing immune complexes. Experimental data indicate that chronic immunization with immune complexes results in the production of T-cell-dependent high-affinity rheumatoid factor (RF) molecules. Depending on the epitope density on the virus and the amount of specific IgG, RF-synthesizing B-cells undergo cell cycle and secrete RF molecules, which can lead to large immune complexes with lattice formation and poor solubility. Synergistic signals of RF-BCR by continuous production of IgG-HCV complexes allow these cells to survive overcoming apoptotic signals. Supervened stochastic genetic accidents provide growth advantage of expanded B cells. Our data define a small subgroup of HCV-positive patients with WM characterized by a serum IgM monoclonal component showing RF activity and tendency to cryoprecipitate. The term 'rheumatoid macrocryoglobulinemia' should be applied to patients with these unique properties.