

[Abstract 21]

AUTOANTIBODY (AAB) ACTIVITY IN WALDENSTRÖM'S MACROGLOBULINEMIA (WM).

Marvin J. Stone¹, Giampaolo Merlini², Virginia Pascual³. Baylor Charles A. Sammons Cancer Center, Dallas, Texas 75246¹, University of Pavia, ITALY², Baylor Institute for Immunology Research, Dallas, Texas, USA³

WM is a B cell neoplasm characterized by monoclonal IgM secretion and marrow infiltration with lymphoplasmacytic cells. It is thought to arise from a post-germinal center B cell which fails to undergo isotype switching. A number of WM IgMs have been documented to possess functional antigen-binding activity, most commonly directed to auto or microbial antigens (Ag). Protein, polysaccharide and lipid Ag have been identified. Monoclonal cold agglutinins (CA) were first described in the 1950s in patients with immune hemolytic anemia. These patients may have or subsequently develop serum IgM M-spikes which can be removed by absorption with red cells bearing the I or i antigen. A characteristic idiotype and V_H gene sequence have been described suggesting that these CA are related to "natural" antibodies. Type II mixed cryoglobulins (MC) with high-titer rheumatoid factor activity were identified in the 1960s. These are monoclonal IgMs with specificity for the Fc fragment of autologous IgG. In some cases each reactant is soluble when isolated; the cryoprecipitating property results from formation of the IgM-IgG immune complex. These patients may have a clinical picture typical of WM. Since 1990 a strong association between hepatitis C virus (HCV) and MC has been demonstrated. HCV has been found in the cryoglobulin and patients with MC have HCV-antibody and RNA present in their sera. Most MC occur in patients with HCV liver disease but without evidence of WM or other non-Hodgkin's lymphoma. It appears that HCV infection results in a spectrum of lymphoproliferative response that is usually limited but, in about 5% of patients, becomes overtly malignant. Therapy with alpha-interferon sometimes induces regression of the monoclonal B cell expansion and MC. A number of monoclonal IgM proteins are AAb to neural elements and are found in patients with peripheral neuropathy. Myelin-associated glycoprotein, gangliosides, and glycosaminoglycan oligosaccharides are some of the Ag identified. Symptoms due to CA, MC and antineural antibodies have been designated "IgM-related" disorders in classification of WM. Because of the Ag-Ab interaction, these patients often present with hemolytic anemia, mixed cryoglobulinemia, or peripheral neuropathy, respectively, at an earlier stage than patients with typical WM without evident clinical clues suggesting the presence of antibody activity associated with their monoclonal IgM. Studies on WM patients have indicated that some have mutated IgM that appears "antigen-driven", others have mutated IgM but the mutations don't fit the pattern described for Ag-driven processes, and a few have unmutated IgMs. In conclusion, some patients with WM produce monoclonal IgM proteins having clearcut antibody activity that influences clinical presentation and natural history of their disease. These "paraproteins" may be generated following exposure to self antigens and certain microbes. They may develop via T-independent as well as T-dependent pathways. Further study of antibody activity in monoclonal IgMs may provide further insights into the pathogenesis of WM.