

NEUROPATHIES ASSOCIATED WITH MONOCLONAL GAMMAPATHIES

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Sir,

in our recent review on neuropathies associated with monoclonal gammopathies¹ we reported on the pathophysiology and the possible direct involvement of monoclonal antibodies in causing the neuropathy. We would like to expound on these aspects not developed in our review because its goal was eminently practical.

As reported in our review, low titers of antibodies directed against several specific nerve antigens (MAG, GM-1 sulfatides) are commonly found in healthy individuals, and polyclonal symptomatic counterparts are also known. These findings imply that an asymptomatic polyclonal autoimmune response involving nerve tissue antigenic determinants occurs in normal individuals and is mediated by so-called *natural autoantibodies*. The latter are usually of the IgM class, polyreactive with low avidity, whose function and significance are still undefined. Other notable examples of polyclonal *natural autoantibodies* are cold agglutinins and rheumatoid factors. If, by chance, one of these cells producing autoantibodies transforms and expands abnormally, a monoclonal autoantibody will emerge and in most instances become symptomatic, thereby determining the condition termed by Marmont *monoclonal autoimmunity*.^{2,3} It is of interest that autoantibodies that are commonly present at low titer may play a pathogenic role at higher concentrations. Differences in antibody specificity and affinity, and differences in antigen conformation, densi-

ty and accessibility may account for difference in clinical symptomatology. As far as neuropathies are concerned, monoclonal anti-MAG IgM antibodies represent a very interesting model. In fact, these antibodies, often associated with a full picture of NHL, present an immunopathogenic mechanism involving complement components that is superimposable on those of classical autoimmunity. The basic mechanisms of autoimmune disease involve breaking down tolerance and eluding immunoregulatory controls, while those of immunoproliferative diseases, to which monoclonal gammopathies belong, involve a series of mutations that include oncogene abnormalities. In this respect monoclonal autoimmunity encompasses and unifies these pathogenetic mechanisms, offering a precious model for improving our understanding of the molecular basis of B cell autoreactivity and transformation. Therefore, in addition to the clinical impact, human monoclonal immunoglobulins with activity against self-antigens also represent a precious research tool.

References

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