Precursor disorders in Waldenström macroglobulinemia (WM): studies of WM susceptibility in high-risk families

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Identification of a precursor lesion for Waldenström macroglobulinemia (WM) is desirable to i) improve understanding of pathogenetic pathways; ii) estimate risk; and iii) develop screening and prevention strategies. Monoclonal gammopathy of undetermined significance (MGUS) has been long recognized as a precursor disorder for multiple myeloma, and there is growing evidence that WM may also have an associated precursor disorder, IgM MGUS. We are interested in understanding the role of IgM MGUS as a risk marker for susceptibility to WM and as a precursor disorder that can progress to WM. We have studied a cohort of familial WM because these families appear to be enriched for IgM MGUS in blood relatives of WM patients. In preliminary cross-sectional studies of 140 first-degree relatives of WM patients from 27 families relatives of WM patients expressed a variety of immunoglobulin (Ig) patterns. IgM MGUS occurred most frequently (n=20, 14.3%), but other Ig patterns, including small-volume IgM MGUS (n=12, 8.6%), polyclonal Ig elevations (n=13, 9.3%), and hypo Ig (n=8, 5.7%) were also seen. In some families, no unusual Ig patterns were found. Longitudinal studies demonstrated that some of these patterns, notably IgM MGUS and IgM polyclonal gammopathy, can evolve to WM or non-Hodgkin lymphoma in some patients. Based on these data, we propose that disordered immune regulation, manifest as a variety of immune abnormalities, may represent a generalized precursor, or susceptible, state. IgM MGUS may arise as either a primary manifestation of this susceptibility or in response to the influence of additional genetic and/or environmental factors, and may in turn predict progression to WM. Large collaborative studies are needed to confirm and extend these findings.