Detection of the somatic mutation MYD88 L265P in Waldenström's Macroglobulinemia and marginal zone B-cell lymphoma using allele-specific PCR

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Waldenström's macroglobulinemia (WM) is a B-cell malignancy characterized by bone marrow (BM) infiltration with lymphoplasmacytic cells and production of an IgM paraprotein. By whole genome sequencing, we recently identified a somatic mutation (L265P) in the MYD88 gene in 90% WM patients. To expand this finding for possible diagnostic testing, an allele-specific (AS) PCR assay was developed with a threshold of detection of 0.08%. DNA from 97 WM patients and 40 healthy donors was analyzed. 87/97 (89.7%) WM patients were positive for MYD88 L265P. By contrast, all healthy donors were negative for MYD88 L265P. Using non-parametric ANOVA, MYD88 L265P positive patients showed greater BM involvement ($p=0.001$), lower serum IgA ($p<0.001$), lower serum IgG ($p=0.011$), and higher serum IgM ($p=0.007$) versus MYD88 L265P negative patients. To explore the potential of using the quantitative AS-PCR method to determine therapeutic effect, bone marrow (BM) biopsies were assessed for seven patients before and after treatment. A high correlation between the readouts of BM involvement and the levels of mutant MYD88 L265P was observed ($R^2=0.90$). These results suggest that MYD88 L265P is a promising biomarker for diagnosis and monitoring disease progression and response to treatment in WM. In addition, we analyzed 46 patients with MZL, which included 21 Splenic (SMZL), 20 Extranodal (ENMZL), and 5 Nodal (NZL) subtypes. 3/46 (6.5%) patients with MZL (1 SMZL; 1 ENMZL; 1 NZL) showed positive for MYD88 L265P. The results demonstrate that the MYD88 L265P mutation can be used to improve differentiation of WM from MZL.