

Angiogenic Support in Waldenstrom's Macroglobulinemia: The Possible Role of Macrophage Inflammatory Protein-1alpha (MIP-1 α)

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Angiogenesis represents an essential step of disease progression in several hematological malignancies. A Mayo Clinic study reported that microvessel density is increased in 30% of patients with Waldenstrom's macroglobulinemia (WM), showed only weak correlation with marrow infiltration and had no impact on patients' survival [Rajkumar *et al*, *Semin Oncol* 2003;30:262-4]. Our group evaluated the serum levels of angiogenic cytokines in 56 WM patients during different disease phases (24 untreated, 20 relapsed/refractory and 12 patients at remission) and in 11 patients with IgM-MGUS. Patients with either WM or IgM-MGUS had increased levels of angiogenin, VEGF, VEGF-A, and bFGF compared with controls. The ratio of angiopoietin-1/angiopoietin-2 was reduced in WM but not in IgM-MGUS. Elevated angiogenin and reduced angiopoietin-1/angiopoietin-2 ratio correlated with adverse disease features [Anagnostopoulos *et al*, *BJH* 2007;137:560-8]. We also found that serum levels of MIP-1 α are elevated in WM [Terpos *et al*, *BJH* 2006;133:301-4]. MIP-1 α is a potent chemoattractant for macrophages and mast cells, which contribute to increased angiogenesis in several malignancies, including multiple myeloma. To further elucidate this finding, we investigated the possible expression of MIP-1 α by WM cells and correlations between MVD, marrow infiltration by WM cells and mast cell numbers in trephine biopsies of 46 patients with newly-diagnosed WM (4 with asymptomatic disease) and of 8 patients with IgM-MGUS. Bone marrow biopsies were studied by immunohistochemistry using antibodies against MIP-1 α , CD34 (endothelial cells), CD68 (PGM-1), and also against CD20, CD21, CD23, CD70,

CD34, CD35, CD56, CD3, CD5, κ/λ , PAX-5, MUM-1, tryptase, MIB and cyclin-D1. Thirteen patients (28%) showed intermediate-grade and 5 (10%) high-grade angiogenesis. Strong correlations were observed between MVD and the bone marrow infiltration by the WM cells ($r=0.507$, $p<0.001$) and between MVD and the number of mast cells into the hot-spots ($r=0.725$, $p<0.0001$). We also found that WM cells were positive for MIP-1 α in all patients with WM (the positive WM cells for MIP-1 α ranged between 80-100%). Both CD20+ and CD138+ cells were positive for MIP-1 α in all WM patients. However, interestingly, plasma cells from the 8 IgM-MGUS patients did not express MIP-1 α in trephine biopsies. The results of our ongoing study show, for the first time in the literature, that WM cell express MIP-1 α , which through the chemoattraction of macrophages and mast cells may contribute to the angiogenesis procedure and reveal possible implications for the biology of WM.