Can flow cytometry be used to discriminate IgM MGUS from WM

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Multiparameter flow cytometry (MFC) has demonstrated its clinical relevance in MGUS, smoldering and symptomatic myeloma. However, immunophenotypic studies on IgM monoclonal gammopathies are scanty, and focus only in patients with WM.

Herein, 244 newly diagnosed patients with an IgM monoclonal gammopathy were studied by MFC. According to the WM workshop, 68 were classified as IgM MGUS, 76 as smoldering and 100 as symptomatic WM. Immunophenotypic studies were performed on bone marrow (BM) samples with a 4-color panel that systematically allowed the identification of B-cells and plasma cells (PC), and their phenotypic characterization for a total of 24 antigens.

As a first step, we analyzed the percentage of B-cells and PC in the whole BM, as well as the percentage of cells with light-chain restriction (according to the isotype of the patient) in both cell compartments. Our results show a progressive increment of B-cells from IgM MGUS to smoldering and symptomatic WM (medians of 2.3%, 8.7% and 12.2%, respectively; P<.001), as wells of light-chain restricted B-cells (75%, 96% and 99%; P<.001). In fact, only 3% of IgM MGUS patients showed ≥10% BM B-cells, in contrast to 34% and 58% of smoldering and symptomatic WM (P<.001). Similarly, only 16% of IgM MGUS patients showed ≥95% light-chain restricted B-cells, in contrast to 67% and 91% of smoldering and symptomatic WM (P<.001). On the other hand, no differences were found for the percentage of BM PC (overall median of 0.3%), but light-chain restricted PC progressively increased from IgM MGUS to smoldering and symptomatic WM (70%, 85% and 90%; P<.001). These results lead us to explore whether the percentages of BM- and light-chain restricted Bcells could predict time to progression (TTP) to symptomatic disease. After a median follow-up of 27 months, IgM MGUS and smoldering WM patients with both ≥10% B-cells and ≥95% light-chain restricted B-cells showed significantly inferior TTP as compared to cases showing only one risk factor and particularly to those without adverse features (3-year rates of 65%, 90% and 100%, respectively; P<.001).

Afterwards, we focused on the immunophenotypic profiles of B-cells and PC among the three patients' groups. Our results show that the mean percentage of CD22+dim B-cells progressively increased from IgM MGUS to smoldering and symptomatic WM (69%, 92% and 88%; P<.001), with similar results being also found for CD25+ (61%, 88% and 90%; P<.001), and IgM+ (88%, 95% and 97%; P=.002) expression, suggesting the emergence of a characteristic Waldenstrom's phenotype (CD22+dim/CD25+/IgM+ B-cells). Moreover, negative expression for CD5, CD10, CD11c and CD103 was found in vast majority of WM patients (≥90%), and this can be particularly useful for the phenotypic distinction between WM and other B-cell chronic lymphoproliferative diseases. Finally, PC showed a normal immunophenotype, but a progressive increment of CD19+, CD20+ and CD45+ cells from IgM MGUS to WM patients was noted, again reflecting a more plasmablastic/immature phenotype in the symptomatic form of the disease.

In summary, our results highlight the potential value of MFC immunophenotyping for the characterization of the Waldenström's clone, as well as for the differential diagnosis and risk of progression of IgM MGUS vs. symptomatic WM. We are currently working with 8-color MFC and preliminary results will be presented.