

Flow cytometric characterization of the clonal bone marrow plasma cell and B-cell compartments in IgM monoclonal gammopathy identified through screening: early findings from iStopMM

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Background: IgM monoclonal gammopathy of undetermined significance (IgM MGUS) is a precursor to Waldenström macroglobulinemia (WM) and related lymphoproliferative disorders. The underlying clone spans the B-cell-to-plasma-cell differentiation continuum, but its composition has been characterized mainly in clinically ascertained, higher-burden disease. We examined the clonal B-cell and plasma cell compartments in IgM monoclonal gammopathy identified through population screening.

Aim: To characterize the clonal plasma cell and B-cell compartments of IgM monoclonal gammopathy in relation to the serum M-protein and MYD88/CXCR4 mutational status.

Methods: Within iStopMM, a population-based screening study for MGUS and randomized trial of follow-up strategies, bone marrow aspirates from participants with an IgM M-protein were analyzed by flow cytometry (three-tube EuroFlow-adapted panel: CD19/CD27/CD38/CD45/CD138 backbone with CD56/CD81/CD117, CD20/CXCR4/CD305, and surface/cytoplasmic IgM/ κ/λ ; median 3.7×10^6 nucleated cells). Clonality was defined by IgM light-chain restriction and assessed within the CD38+CD138+ plasma cell compartment and the mature B-cell compartment. Clonal compartment sizes (% of nucleated cells) were correlated (Spearman) with the serum IgM M-protein, and the plasma cell κ/λ ratio with the FLC ratio ($\log_2$). MYD88^{L265P} and CXCR4 were assessed by NGS of bone marrow DNA (sensitivity $\geq 3\%$ VAF).

Results: Of a planned 120, 27 participants with an IgM M-protein (21 MGUS, 5 SWM, 1 WM) have been included; median IgM M-protein 1.8 g/L (range 0.1-35.8). A clonal population was detected in 22/27 (81%); the 5 without had low M-protein (median 0.1 g/L). Three clonal architectures were observed: plasma cell plus B-cell (n=13), plasma-cell-only (n=9), and none (n=5). When both were present, the clonal B-cell compartment was larger than the plasma cell compartment (median 16-fold), and the two sizes were not correlated ($\rho=0.18$, ns, n=13).

The CD38+CD138+ clonal plasma cells displayed a WM-associated phenotype: CD27+, CD81+, cytoplasmic IgM+, CD56-, CD117-, CD305-, CD45 variable; CD19 and CD20 were negative in 27% and 59%.

The percentage of clonal plasma cells correlated with IgM M-protein concentration ($\rho=0.78$, $p<0.001$, $n=22$). Within the 13 samples containing both compartments, the plasma cell compartment remained correlated ($\rho=0.57$, $p<0.05$), whereas the clonal B-cell compartment did not ($\rho=0.29$, ns). The plasma cell κ/λ ratio correlated with the serum FLC ratio ($\rho=0.76$, $p<0.001$; $n=27$).

MYD88^{L265P} was detected in 7/27 (26%) and CXCR4 in 3/27 (11%; all with MYD88 and at lower VAF). MYD88 detection was associated with higher clonal burden (AUC 0.99), with clonal B cells present in all mutated cases.

Conclusions: In this cohort of individuals with IgM monoclonal gammopathy detected by screening, all detectable clones included a plasma-cell-differentiated component whose size correlated with serum IgM M-protein, while MYD88^{L265P} was detected only in the larger B-cell-containing clones. These preliminary findings indicate heterogeneous clonal architecture along the B-cell-to-plasma-cell continuum, in which the plasma cell compartment reflects secretory output, while MYD88 detection identifies higher-burden clones, more likely to have prominent B-cell involvement. Limitations include the small cohort size and the inherent difficulty of identifying small B-cell clones against a polyclonal IgM background. Immunophenotypic dissection of the clonal architecture in IgM MGUS may provide insight into biological heterogeneity and complement conventional serological and molecular workup.

Table. Characteristics of the study cohort.

Characteristic	Overall (n=27)	MGUS (n=21)	SWM/WM (n=6)
Age, median (range)	71 (55-83)	71 (55-82)	77 (58-83)
Male sex, n (%)	13 (48)	10 (48)	3 (50)
IgM M-protein, g/L	1.8 (0.1-35.8)	0.7 (0.1-11.4)	7.7 (0.1-35.8)
Involved/uninvolved FLC ratio*	1.58 (0.66-21.9)	1.28 (0.66-16.5)	3.52 (1.22-21.9)
Flow cytometry of BM			
Clonal population detected, n (%)	22 (81)	16 (76)	6 (100)
PC+B / PC-only / none	13 / 9 / 5	7 / 9 / 5	6 / 0 / 0
Clonal PC, % nucleated	0.16 (0.02-1.48)	0.15 (0.02-0.46)	0.28 (0.06-1.48)
Clonal B cells, % nucleated	6.58 (0.14-36.3)	2.35 (0.14-8.15)	8.41 (0.46-36.3)
NGS of BM			
MYD88 ^{L265P} , n (%)	7 (26)	2 (10)	5 (83)
CXCR4 mutated, n (%)	3 (11)	1 (5)	2 (33)

The SWM/WM column combines 5 SWM and 1 WM

*Involved light chain defined by serum immunofixation

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