

IgM MGUS Diagnostic Challenges: Navigating ICC and WHO Classification Discrepancies

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Introduction

Diagnostic criteria for IgM MGUS and Waldenström macroglobulinemia (WM) differ between the WHO-5 classification and the International Consensus Classification (ICC). While both classifications emphasize clone size and recommend testing for the *MYD88* L256P mutation, they differ in bone marrow (BM) infiltration thresholds. The ICC criteria classifies the presence of lymphoplasmacytic B-cell aggregates and clonal B or plasma cells in a BM biopsy as WM, regardless of infiltration percentage. Conversely, WHO-5 maintains a 10% threshold to differentiate WM from IgM MGUS. This study aimed to determine if these criteria lead to divergent diagnoses in patients with low-burden clones ($\leq 10\%$) and to evaluate the performance of diagnostic techniques for small clone detection.

Methods

This single-center, academic, study analyzed patients with an IgM M-protein undergoing BM examination within a structured MGUS care pathway. This pathway prioritizes the early detection of small-clone diseases, such as AL amyloidosis, POEMS, and clinically significant MGUS, establishing a low threshold for performing BM biopsy. Diagnostic modalities performed on BM biopsies included morphological assessment, immunohistochemistry (IHC), and droplet digital PCR (ddPCR) for the *MYD88* mutation (detection limit 0.04%). Multiparameter flow cytometry (FC) was performed on BM aspirates. B-cell receptor rearrangement assays were not conducted.

Results

From April 2021 to December 2025, 298 patients were evaluated, of whom 251 (84,2%) were diagnosed with MGUS and 84 of these 251 patients had an IgM M protein (33,5%). BM biopsies were performed in 35 of the 84 patients (41.7%), mainly based on symptoms and laboratory abnormalities. Elevated IgM levels were seen in 22 of the 35 patients (normal values 0.4-2.3 gr/L). In 11 (31.4%) BM biopsies clonal plasma cells and/or increase of B cells with or without aggregates were observed; the remaining 24 biopsies were assessed as normal. Lymphoplasmacytic aggregates were seen in 5 of the 11 (45.5%) positive BM biopsies, which would qualify them as WM in the ICC criteria. The 11 patients with clonal infiltration had higher mean serum IgM levels compared to the 24 negative patients (11,7 gr/L vs 3,4 gr/L). Very small, potentially reactive aggregates were noted in 5 of the 24 normal biopsies; a *MYD88* mutation was detected in 3 of them (variant allele frequency [VAF] range 0.35–1.7%). Overall, ddPCR detected *MYD88* mutations in 24 biopsies (68.6%), was negative in 9, and not performed in 4. The VAF was $<5\%$ in all cases (maximum 4.1%). FC did not enhance diagnostic sensitivity and showed discordance with histology in 2 patients; one was *MYD88* positive and had clonal B cells with CLL phenotype, the other patient was *MYD88* negative with clonal B cells.

Conclusion

Applying ICC criteria upstages 14.3% of patients (5 out of 35) from IgM MGUS to WM and when BM abnormalities are seen, this increases to 45.5%. Furthermore, ddPCR was the most sensitive diagnostic technique to detect a neoplastic cell proliferation, detecting the *MYD88* mutation in 63%

of patients compared to 31.4% using morphology and IHC combined. This highlights the vital role of highly sensitive molecular testing for low-burden clones.

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