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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Immune Cells, Cytokines, and Gut Microbiota Landscape Along Monoclonal Gammopathy of Undetermined Significance (MGUS) to Multiple Myeloma (MM) Evolution

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Introduction: Multiple myeloma (MM) is an incurable hematologic cancer characterized by abnormal plasma cell growth in the bone marrow (BM). It is preceded by two premalignant conditions: monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM). Understanding the transition from MGUS to MM is crucial for better risk stratification, early interventions, and targeted treatments. This study aims to gain insights into immunological changes and fecal microbiota variations along the MGUS to MM transition.
Methods: To comprehensively evaluate the immune composition (myeloid/lymphoid T/B/NK subpopulations and immune checkpoint distribution) in both bone marrow (BM) and peripheral blood (PB), we designed six 10-color custom and two 8-color flow cytometry panels. We analyzed samples from 13 MGUS, 12 SMM, and 63 newly diagnosed MM patients. Additionally, we evaluated cytokine/chemokine abundance in BM and PB using a 48-plex Luminex plate on 72 samples from the same MGUS, SMM, and MM patients, along with 4 healthy donors (HD). Furthermore, we performed fecal microbiome profiling on samples from 3 MGUS, 6 SMM, and 9 MM patients to investigate potential relationships between bacterial composition and MM evolution. Statistical analysis was performed in R by using specific packages (such as FlowCT).
Results: Through unsupervised analysis of T cells by flow cytometry, we identified a significant increase in circulating TEMRA CD8 T cells, mostly for CD57+ cells (mean, 7.5% for MGUS vs 20.1% for SMM vs 21.6% for MM; $p<0.05$) and a significant reduction in naïve CD8 T TIGIT+ cells (mean, 12.4% for MGUS vs 5.98% for SMM vs 4.16% for MM; $p<0.001$) and naïve CD8 T TIGIT+ TIM3+ (mean, 2.18% for MGUS vs 1.24% for SMM vs 1.17% for MM; $p<0.001$). Regarding CD4 T subsets, we observed a reduction in BM effector memory phenotype along disease evolution (mean, 7.07% for MGUS vs 4.54% for SMM vs 3.72% for MM; $p<0.05$). Interestingly, we confirmed the increase of BM CD4 T cells production of IL17 (mean: 6.7% for MGUS vs 22% for MM; $p<0.05$) in MM patients compared to those with MGUS. In the context of myeloid cell subsets, circulating non-classical monocytes expressing HLA-DR and CD11c (mean, 1.45% for MGUS vs 0.95% for SMM vs 0.69% for MM; $p<0.05$) as well as granulocytes (mean, 74.18% MGUS vs 73.86% SMM vs 65.59% MM; $p<0.05$) were found to be reduced along MM progression. No major differences were observed for other evaluated lineages. Regarding cytokines and chemokines, a concurrent decrease in GM-CSF, IFN-a2, IFN-g, IL-1b, IL-2, IL-2Ra, IL-3, IL-10, IL-13, and MCP-1/CCL2 levels within the BM plasma throughout MM progression was observed, thus supporting a global reduction in myeloid function as well as in T cell effector activity. Moreover, PDGF-BB, IFN-a2, IL-16, and IL-8 decrease was observed in PB plasma along MM progression. Lastly, while no differences were observed in term of alpha and beta diversity, we observed an overall increase in total abundance of fecal bacteria along MM evolution (maybe related to loss of myeloid/lymphoid control according to what previously described), with several bacterial genus significantly over-represented in MM patients, including *Bariatricus, CAG-83, Alistipes, Bifidobacterium, Streptococcus, Ruminococcus D, Slackia A, and Coprococcus A*, while others (such as *Parabacteroides B*) was found to be more represented in MGUS and SMM patients. The analysis of *phyla* abundance indicated *Firmicutes D* and

Lactobacillales as more abundant in MM patients, while *Actinobacteriota* dominated in SMM patients, and *Proteobacteria* and *Bacteroidota* were more prominent in MGUS patients.
Conclusions: Overall, this study demonstrated a progressive impairment of both myeloid and lymphoid compartment in term of cellular composition, cytokine production and release and control over gut microbiome. Recovering from T cell exhaustion and IL17 production remains a major challenge for these patients.

Disclosures No relevant conflicts of interest to declare.

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