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From Silent Clones to Myeloma: Unraveling the Genetic Clues Behind MGUS and Smoldering Myeloma

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are distinct precursor conditions within the disease progression spectrum that can potentially lead to multiple myeloma (MM). This analysis elucidates the marked disparity in progression kinetics between these precursor states—with MGUS demonstrating an annual conversion rate of approximately 1% versus the substantially elevated 10-15% progression rate observed in SMM—thus emphasizing the critical necessity for precise risk stratification methodologies. The molecular pathogenesis underlying progression encompasses complex genetic and epigenetic perturbations, including chromosomal aberrations, somatic mutations, and dysregulation of epigenetic regulatory mechanisms such as DNA methylation patterns and histone modification profiles. The incorporation of molecular biomarkers, particularly recurrent chromosomal translocations and driver gene mutations, into prognostic algorithms has demonstrably enhanced the discriminatory capacity to identify high-risk patient subsets who may derive benefit from intensified surveillance protocols and preemptive therapeutic interventions. The translational integration of comprehensive genetic and genomic profiling into clinical decision-making paradigms for MGUS and SMM patients carries profound implications, facilitating individualized surveillance strategies and potentially enabling precision medicine approaches that may interrupt or slow down the advancement to symptomatic multiple myeloma.

Introduction

Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM) are recognized as precursor conditions that may eventually progress to Multiple Myeloma (MM), a malignant cancer of plasma cells. MGUS is marked by the presence of monoclonal proteins in the blood or urine but lacks evidence of end-organ damage. In contrast, SMM is defined by higher levels of monoclonal proteins and a greater tumor burden. Understanding how these early stages evolve into full-blown MM is critical for improving risk prediction and developing early intervention strategies. A central area of research focuses on unraveling the genetic and molecular events that drive this progression, as these insights can aid in more effective monitoring and prevention (Zuern et al., 2024; Firdaus & Li, 2024; Bustin & Jellinger, 2023).

A key factor in the transformation from MGUS to MM is the gradual buildup of chromosomal abnormalities. While MGUS often begins with a single chromosomal abnormality—such as hyperdiploidy or translocations involving the immunoglobulin heavy chain (IgH) region—further progression involves additional genetic alterations (Dhodapkar, 2016; Barwick et al.,

2019; van Nieuwenhuijzen et al., 2018). These include copy number changes and mutations in genes involved in cell cycle regulation, DNA repair, and epigenetic control. Commonly observed mutations in genes like KRAS, NRAS, TP53, and BRAF activate pathways such as MAPK and PI3K/AKT, which are pivotal in the development of multiple myeloma (Pérez-Escurza et al., 2023).

Beyond genetic mutations, epigenetic changes are also instrumental in disease progression. Altered DNA methylation and histone modification patterns can disrupt gene expression, facilitating the shift from MGUS to MM (Amodio et al., 2017; Sharma et al., 2010). Researchers have identified unique epigenetic profiles associated with increased risk of progression, underscoring their significance in the disease's biology. Consequently, identifying genetic and epigenetic biomarkers has become a primary goal, with risk assessment models increasingly incorporating these elements to pinpoint individuals at high risk who may benefit from intensified surveillance or preemptive therapy (Mateos et al., 2020; Jeremias et al., 2020; Verma et al., 2006).

Next-generation sequencing (NGS) has revolutionized our understanding of the genetic complexity within MGUS and SMM, uncovering clonal heterogeneity even in these early disease stages (Ho et al., 2020; Bolli et al., 2020). The presence of subclones carrying distinct mutations is linked to a higher likelihood of advancing to MM, emphasizing the importance of tracking clonal evolution. Additionally, the bone marrow microenvironment including osteoclasts, osteoblasts, and immune cells supports the survival and growth of malignant plasma cells. Disruptions within this niche are associated with disease advancement, indicating that therapies targeting the tumor-stroma relationship could be beneficial (Lakshman et al., 2018; Valkenburg et al., 2018).

Current research is aimed at developing treatments that address the genetic and epigenetic drivers of MGUS progression. Targeted therapies, including inhibitors of key signaling pathways and agents that modulate epigenetic activity, have shown potential in early trials. Immunotherapies, such as monoclonal antibodies and CAR T-cell therapy, are also being explored for patients with high-risk MGUS and SMM. Ultimately, the accumulation of genetic and epigenetic alterations is a crucial determinant in the transition to MM. Continued investigation into these mechanisms is essential for refining risk models and creating targeted approaches to prevent or delay the onset of this malignancy (Fernandez de Larrea et al., 2018).

Methods

A thorough literature review was undertaken to explore monoclonal gammopathy, smoldering multiple myeloma, and multiple myeloma. The search strategy utilized a range of relevant keywords, including "monoclonal gammopathy of undetermined significance," "MGUS," "smoldering multiple myeloma," "SMM," "multiple myeloma," "MM," "disease progression," "risk stratification," "biomarkers," and "treatment guidelines." These terms were systematically applied across several major electronic databases, including PubMed, Embase, Web of Science, Scopus, and the Cochrane Library.

To be included, studies had to involve human participants, be published in English, and address topics such as the pathophysiology, diagnosis, progression, risk stratification, or clinical management of MGUS, SMM, and MM. Exclusion criteria ruled out case reports involving fewer than ten patients, non-English publications, and studies using animal models. Additional manual searches were performed by examining reference lists of relevant studies, reviewing clinical guidelines from prominent hematology organizations, and exploring “related articles” suggested by key publications.

The study selection process was conducted independently by two reviewers, with a third reviewer resolving any disagreements. Data extraction was centered on essential themes,

including diagnostic criteria, progression risk factors, biomarkers, imaging modalities, treatment approaches, and patient outcomes throughout the spectrum from MGUS to MM.

Result and Discussion

Epidemiology of MGUS and Smoldering Myeloma

Monoclonal gammopathy of undetermined significance (MGUS) is a relatively prevalent condition, affecting about 3–4% of the general population. Its occurrence increases with age, with rates rising to 5–8% among individuals over 70 years old. In comparison, smoldering multiple myeloma (SMM) is much less common, impacting approximately 0.5–1% of people. Annually, MGUS has an estimated incidence of 3–4 cases per 100,000 individuals, whereas SMM occurs at a lower rate of around 0.5–1 case per 100,000 people. These figures underscore the greater prevalence of MGUS relative to the rarer SMM (de Daniel et al., 2024).

Several risk factors are associated with the development of MGUS and SMM. Age is the most significant contributor, with both conditions more frequently diagnosed in older populations. Additional risk factors include male gender, African American ethnicity, and a family history of plasma cell disorders. Moreover, chronic inflammatory conditions and autoimmune diseases may also elevate the risk, possibly due to persistent immune activation and dysregulation (de Daniel et al., 2024; Mateos et al., 2020; Zuern et al., 2024).

While both MGUS and SMM are considered precursor stages to multiple myeloma (MM), they differ in several key aspects. MGUS is characterized by a low level of monoclonal protein (M-protein) in the blood or urine—typically under 3 g/dL—and by the absence of end-organ damage, such as hypercalcemia, renal impairment, anemia, or bone lesions. In contrast, SMM presents with higher M-protein levels (often above 3 g/dL) and a greater tumor burden, evidenced by an increased percentage of plasma cells in the bone marrow. The likelihood of progression to MM varies markedly between the two conditions. MGUS has a relatively low annual progression risk of about 1%, while SMM progresses to MM at a much higher rate, estimated at 10–15% per year. This substantial difference highlights the need to clearly differentiate between MGUS and SMM, as patients with SMM typically require closer surveillance and may benefit from proactive therapeutic approaches. Recognizing these epidemiological trends is essential for identifying high-risk individuals and guiding their clinical management effectively (Bustoros et al., 2020; Stoffel et al., 2023; Wong et al., 2022).

Biological Mechanisms Underlying MGUS and Smoldering Myeloma

The origins of MGUS and smoldering multiple myeloma (SMM) lie in the clonal expansion of plasma cells within the bone marrow. In MGUS, this proliferation is relatively mild, resulting in the production of low levels of monoclonal protein without causing damage to organs. In contrast, SMM involves a higher burden of plasma cells and elevated monoclonal protein levels, indicating more extensive infiltration of the bone marrow.

The progression from MGUS and SMM to multiple myeloma (MM) is driven by a series of complex genetic and epigenetic alterations. Disruptions in critical signaling pathways—such as MAPK and PI3K/AKT—play a key role in promoting disease progression. Equally important is the bone marrow microenvironment, which interacts closely with clonal plasma cells. Various components of this environment, including osteoclasts, osteoblasts, and immune cells, form a supportive niche that nurtures tumor growth. Bone marrow stromal cells release cytokines and growth factors like interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), which enhance plasma cell survival and proliferation. Additionally, changes in the immune landscape of the bone marrow contribute to immune evasion, allowing malignant cells to expand unchecked (Cowan et al., 2023; Botta te al., 2021; Kouroukli et al., 2022).

As MGUS or SMM progresses toward MM, clonal plasma cells accumulate further genetic mutations and chromosomal abnormalities, leading to increased genomic instability and the

emergence of more aggressive subclones. These alterations further disturb signaling networks, promote tumor cell resilience, and reinforce their interaction with the microenvironment. The shift to overt MM is also marked by heightened osteoclast activity, which contributes to the development of bone lesions, and a weakening of the immune system's ability to combat tumor cells. Gaining a deeper understanding of these underlying biological mechanisms is crucial for advancing risk prediction and developing precision therapies. By identifying the genetic, epigenetic, and microenvironmental drivers of disease progression, researchers can discover new biomarkers and therapeutic targets—ultimately improving the clinical management and outcomes for patients with MGUS and SMM (Lonial et al., 2020; Desantis et al., 2022).

Genetic Alterations and Biomarkers in MGUS and Smoldering Myeloma [A4]

The onset of MGUS and SMM is closely linked to specific genetic alterations, including both mutations and chromosomal changes. In the early stages of MGUS, common genetic abnormalities include hyperdiploidy and translocations such as t (11;14) and t (4;14), which disrupt genes involved in regulating cell growth and survival. These alterations are considered early events in the development of plasma cell disorders. As the condition advances from MGUS to SMM, additional genetic mutations tend to emerge. These include changes in genes such as KRAS, TP53, NRAS, and BRAF, all of which activate oncogenic pathways that promote cell proliferation and resistance to apoptosis. Chromosomal changes like deletions of chromosome 13 (del [13]), deletion of 17p (del [17p]), and gain of 1q also play a role in disease progression. These abnormalities contribute by either amplifying oncogenes or eliminating tumor suppressor genes, thereby increasing genomic instability and supporting the development of more aggressive cellular clones (Manasanch et al., 2019; Singh et al., 2025; Vasudevan et al., 2021).

Ongoing research is focused on refining the use of genetic biomarkers to better predict the risk of progression from MGUS or SMM to multiple myeloma (MM). Next-generation sequencing (NGS) has provided valuable insights into the genetic complexity of these conditions, uncovering patterns of clonal diversity and the emergence of distinct subclones. Certain genetic features—such as t (4;14), t (14;16), and mutations in TP53 or BRAF—have been linked to a higher likelihood of progression to MM. Tracking the evolution of these subclonal populations may enhance prognostic precision and inform clinical management strategies. As genetic research continues to advance, it may become increasingly possible to identify individuals at higher risk of progression with greater accuracy. This would allow for more rigorous monitoring and the implementation of early intervention strategies, potentially delaying or even preventing the development of overt multiple myeloma (Zuern et al., 2024; Lehmann et al., 2023).

Predicting Progression to Multiple Myeloma[A6]

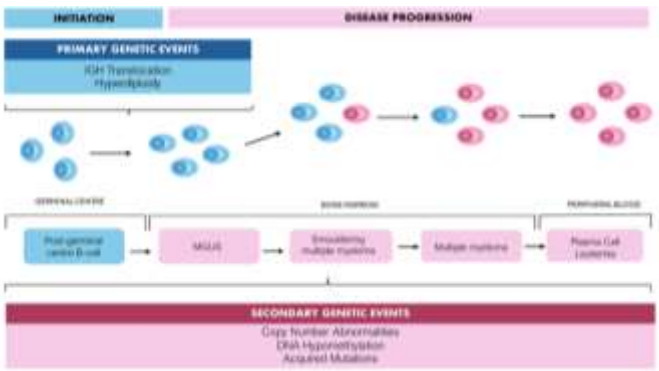

Figure 1. Genetic Mechanisms and Clinical Progression in Multiple Myeloma Development

Due to the varying risks of progression from MGUS and SMM to multiple myeloma (MM), accurately predicting disease advancement is essential for optimizing patient care. Researchers are actively developing risk stratification models that integrate both clinical and genetic variables to better assess an individual's risk of progression. One widely adopted model is the Mayo Clinic risk stratification system, which classifies MGUS patients into low-, intermediate, and high-risk categories. This classification is based on factors such as serum M-protein concentration, the type of monoclonal protein, and the ratio of involved to uninvolved free light chains. The Mayo model has proven effective in identifying MGUS patients at elevated risk for progression to MM. For SMM, more detailed models are being created, incorporating both clinical indicators and genetic biomarkers to enhance prognostic accuracy (Cowan et al., 2023; Fernandez de Larrea et al., 2018; Lobato-Delgado et al., 2022).

Another prominent system, the Spanish Myeloma Group (GEM) risk model, includes variables like the percentage of bone marrow plasma cells, the presence of chromosomal abnormalities such as del (17p) and gain of 1q, and serum M-protein levels to stratify patients. In terms of genetics, specific chromosomal translocations such as t(4;14) and t (14;16)—and mutations in genes like KRAS, NRAS, and TP53 have been strongly associated with an increased risk of disease progression in both MGUS and SMM (Ferla et al., 2024).

The use of next-generation sequencing (NGS) has significantly advanced the understanding of clonal dynamics in these precursor conditions (Kumar et al., 2024; Desai et al., 2022). NGS allows for the detection of clonal heterogeneity and subclonal evolution, offering a more detailed genetic profile. These insights help identify specific subclones with mutations that are predictive of progression to MM. While traditional clinical indicators—such as M-protein levels and plasma cell counts remain important, the addition of genetic biomarkers has markedly improved the precision of risk prediction models. Comparative studies have demonstrated that risk models incorporating genetic data outperform those based solely on clinical criteria, making it easier to pinpoint high-risk individuals who might benefit from more frequent monitoring or early therapeutic interventions. Furthermore, genetic-based models are better equipped to track disease evolution over time, capturing the development of aggressive subclones that signal a shift toward malignancy (Nadeem et al., 2019; Peneder et al., 2021).

Incorporating genetic information into risk prediction tools has become increasingly vital in the management of MGUS and SMM. This integration allows for more personalized risk assessments and enables clinicians to tailor follow-up and treatment plans more effectively. Ultimately, the use of such models helps delay or even prevent the progression to symptomatic multiple myeloma by facilitating early, targeted intervention (Brighton et al., 2019; Rodriguez-Otero et l., 2021; Dutta et al., 2022).

Clinical Implications of Genetic Information in Patient Management

The incorporation of genetic and genomic information into the clinical care of patients with MGUS and SMM holds substantial promise for improving outcomes. Identifying high-risk individuals based on their genetic profiles allows healthcare providers to tailor monitoring and treatment plans more effectively. Patients with high-risk genetic alterations can be placed under more intensive surveillance, which may include frequent assessments of serum M-protein, bone marrow evaluations, and advanced imaging. This proactive approach facilitates the early detection of disease progression and supports timely clinical decision-making. For those at elevated risk, early therapeutic interventions such as targeted treatments or immunotherapies may be considered. These approaches are aimed at eradicating or suppressing the most dangerous clones before they progress to symptomatic multiple myeloma. Current clinical trials are investigating the effectiveness of such early treatment strategies in high-risk MGUS and SMM patients, and initial findings are encouraging (Wang et al., 2020; Ferla et al., 2024).

Advances in genetic research have also opened the door to precision medicine in plasma cell disorders. Mutations in genes like *KRAS* and *NRAS* have led to the development of MEK inhibitors, while alterations in *TP53* are being explored for therapies that act on the p53 signaling pathway. Similarly, chromosomal abnormalities such as *del(17p)* and *1q gain* have inspired the development of treatments targeting these genomic events or their downstream effects. These targeted therapies are designed to selectively eliminate high-risk malignant cells while minimizing the side effects typically seen with conventional chemotherapy (Zavidij et al., 2020; Najafi et al., 2021).

Despite significant advancements, there are still gaps in our understanding of how best to apply genetic insights in clinical settings. Much of the existing research has been retrospective and conducted on small, heterogeneous cohorts. There is a clear need for larger, prospective studies to validate current genetic biomarkers and to further refine predictive models. Deeper investigations into clonal evolution and the dynamics of subclonal populations will also be essential for identifying new therapeutic targets and enhancing risk assessment (Robinson et al., 2023).

The use of next-generation sequencing (NGS) has been transformative in uncovering the complex genetic landscape of MGUS and SMM. NGS enables personalized risk profiling and aids in the development of individualized treatment approaches. Looking ahead, integrating genetic findings with other diagnostic tools such as imaging results and immune profiling could yield more comprehensive and accurate risk stratification models. Moreover, the application of artificial intelligence (AI) and machine learning is beginning to play a role in interpreting complex genetic and clinical data. These technologies have the potential to uncover subtle patterns and interactions that may otherwise go undetected, further enhancing the precision of risk prediction and guiding more effective patient management strategies.

Conclusion

Integrating genetic and genomic information into the clinical management of MGUS and SMM has the potential to significantly transform the approach to these precursor conditions. By using genetic profiling to identify patients at higher risk of progression, clinicians can tailor monitoring protocols and consider early treatment strategies aimed at preventing or delaying the development of multiple myeloma. This review underscores the pivotal role that genetic and epigenetic alterations play in the initiation and advancement of MGUS and SMM, reinforcing the need to apply these insights in clinical settings. Continued research in this field will be essential for developing more effective approaches to delay or prevent the progression to full-blown multiple myeloma.

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