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Monoclonal Gammopathy of Undetermined Significance and Smoldering Myeloma

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Abstract

Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Myeloma (SMM) describe pre-malignant conditions that are defined by the presence of monoclonal immunoglobulin production. They are found in up to 3% of individuals over the age of 50 with a rate of progression to multiple myeloma or other related malignancy of approximately 1% per year. Accurate diagnosis and risk-stratification are paramount to prevent end-organ damage and determine follow-up intervals. With the data currently available, treatment for MGUS is not recommended. Patients with newly diagnosed high- risk SMM should be referred to a centre and therapy with lenalidomide plus/minus dexamethasone for 2 years or participation in a clinical trial should be discussed.

Manuscript

Monoclonal Gammopathy of Undetermined Significance (MGUS) is defined as the presence of a Monoclonal Protein (M-protein), which is detected by either serum or urine protein electrophoresis, or unexplained Free Light Chain (FLC) excess in the absence of a monoclonal Immunoglobulin Heavy chain (IgH), with serum monoclonal protein levels <3 g/dL and less than 10% clonal plasma cells on bone marrow biopsy [1]. Additionally, the definition of MGUS requires the absence of symptoms of clinical Multiple Myeloma (MM) which entail end-organ damage including hypercalcemia, renal dysfunction, anemia, and/ or lytic bone disease (CRAB criteria).

Plasma cells are terminally differentiated B-lymphocytes which derive from post-germinal center B-cells [2]. Fluorescence *in Situ* Hybridization (FISH) has identified chromosomal abnormalities in the development of MGUS such as aneuploidy and hyperploidy [3,4]. Translocations involving the IgH locus on chromosome 14q32 and one of five partner chromosomes have been identified in approximately 50% of patients with MGUS [5]. Besides IgH translocations, chromosome abnormalities known to be specific for myeloma have been detected (*RB1* (13q14) deletion, 1q-gain, hyperdiploidy) but their frequency is lower in MGUS than in MM [6]. Of note, *TP53* and *MYC* aberrations were not discovered which suggests that these events could occur later in the course of the disease and may lead to MGUS progression to more advanced stages [7].

MGUS is found in approximately 5% of the population above the age of 50 but its incidence varies greatly based on ethnicity, with higher levels detected in Northern Europe and North America compared to those in Asia [8-10]. MGUS is significantly more common in black individuals, and more often presents with features related to a higher risk of progression to MM [11]. The incidence also increases with age ranging at 3-4% of the population aged 50 to 60 years compared to approximately 10% among 80 year old individuals [12]. All cases of MM evolve from MGUS [13,14]. MGUS progresses to MM or a related malignancy at a rate of 1% per year but the exact risk is determined by the type and concentration of the M-protein, serum FLC ratio, plasma cell infiltration of the bone marrow, proportion of clonal plasma cells, and presence of immunoparesis. The three major risk factors comprise high serum M-protein level (≥1.5 g/dL), an abnormal serum FLC ratio (i.e., the ratio of affected FLC to unaffected FLC in the serum), and non-IgG MGUS [15]. Based on this stratification model, the presence of all three factors classifies as high-risk MGUS, two factors high-intermediate-risk MGUS, one factor low-intermediate- risk MGUS, and the absence of all three factors constitutes low-risk MGUS. Notably, age, sex, hemoglobin values, serum creatinine, serum albumin, hepatosplenomegaly, and quantitative measurements of a monoclonal urinary light chain do not qualify as predictors of MGUS progression. Also, earlier onset of MGUS does not affect the course of the disease [16]. However, it is well known that some patients with MGUS can progress rapidly despite their apparent low disease burden [17,18]. The advent of newer technologies including low-input Whole-Genome Sequencing (WGS) technology allowed to characterize differences in the genomic landscape and the acquisition of genomic events between clinically stable and progressive cases of MGUS [19].

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The distribution of genetic events revealed remarkable differences and identified 2 biologically and clinically distinct entities of asymptomatic MGUS: one entity with a sufficient number of genomic events to develop malignant potential and which is related to progressive disease and another entity with a lower burden of genetic events characterized by a prolonged, indolent, and clinically stable course. Thus, WGS has the potential to precisely distinguish stable from progressive precursor conditions in low disease burden states [20].

Screening for MGUS in the general population is not recommended due to the lack of evidence supporting the clinical benefit of early detection [21]. Thus, MGUS is often discovered incidentally. Testing for monoclonal protein is regularly performed for signs and symptoms not typically associated with lymphoplasmocytic malignancies such as neuropathy, renal disease, anemia or bone disorders [22]. However, 3 recent observational studies have concurrently revealed that patients with MM and a prior history of MGUS display approximately 15% better overall survival when compared with MM patients without previous knowledge of MGUS [23-25]. This suggests that an improvement in overall survival was achieved by regular clinical follow-up of MGUS which lead to fewer patients with symptomatic end-organ damage and, therefore, less morbidity at the time of MM diagnosis. Similarly, more recent results from the iStopMM study showed that active screening of MGUS patients helped to identify more patients with progression than by following patients under current guidelines [26]. Survival data of the trial is not yet mature but until then, screening of high-risk patients with two or more first-degree relatives diagnosed with MM, or other plasma cell dyscrasias like AL-amyloidosis, or Waldenstroem's disease may be beneficial [27].

Despite recent phase 3 trials, there is still insufficient data to support intervention in the MGUS setting when considering the low risk of progression and the toxicity derived from therapies used for MM. Thus, initiating, disease-specific treatment with chemoimmunotherapy or targeted therapy is currently not indicated. However, it is indispensable to follow-up patients together with laboratory evaluations focused on the individual risk of progression. These should include serum protein electrophoresis, serum FLC assessment, complete blood count, as well as serum calcium and serum creatinine [27]. Routine imaging studies and bone marrow assessment should not be performed unless there are signs of clinical or laboratory progression. The IMWG recommends follow-up for low-risk patients at 6 months from the date of diagnosis and then every 2–3 years if the disease is stable. Patients with higher-risk disease should be followed annually after an initial 6-month follow-up from diagnosis [21]. As more clinical trials are currently investigating daratumumab, cancer vaccines, rifaximin or drug repurposing, patients should be referred to a centre and clinical trial participation should be discussed [28,29].

Smoldering Multiple Myeloma (SMM) lies between MGUS and MM yet is still asymptomatic without CRAB-criteria. It is distinguished from MGUS by the M-protein concentration (≥3 gm/dL) and percentage of clonal plasma cells in the bone marrow (10– 60%) [30]. Light chain SMM is a subtype which is characterized by monoclonal FLC excess without expression of an intact IgH M-protein and by the presence of ≥500 mg/24h of monoclonal FLC on urine protein electrophoresis.

SMM can be detected in approximately 0.5% of the population above the age of 40 years [31]. It is important to differentiate SMM from MGUS because the risk of progression from SMM to MM is 10 times higher than that of MGUS in the first 5 years after diagnosis with a rate of about 10% per year, 3% per year over the next 5 years, and 1.5% per year ther eafter [32]. Thus, MGUS and SMM should be counseled and followed differently.

With a decreasing risk of progression after diagnosis, SMM is currently understood to be a heterogenous entity rather than a true intermediate between MGUS and MM [33]. But by this definition, SMM would include both patients with MGUS and actual MM. Thus, the strategic approach toward SMM has changed [34]. To identify SMM patients who will in fact develop end-organ damage within 2 years after diagnosis, three biomarkers (SLiM- criteria) were validated: clonal plasma cells in the bone marrow ≥60%, a ratio of involved to uninvolved serum FLC ≥100 (provided involved FLC level is ≥100 mg/L), and more than 1 focal lesion (5 mm or more in size) on magnetic resonance imaging. Each of these criteria allows classifying patients at high risk of progression within 2 years (approximately 80%) and was thus considered Myeloma Defining Events (MDE) [30]. This approach permitted therapy to be introduced before the onset of significant end-organ damage. However, newer data suggests that while the FLC ratio ≥100 is related to a high risk of progression, it does not indicate an imminent risk, which is defined by the IMWG as median time to progression of 12 months and a 2-year progression rate of at least 80%. Instead, it was shown that select patients with an FLC ratio ≥100 can be followed for multiple years without developing progressive disease. Notably, some never progressed despite long-term follow-up. These findings suggest that the FLC dynamic over time as well as other high-risk features should be considered in the decision to initiate treatment when the FLC ratio ≥100 is the only MDE [35].

Therefore, identifying patients with a 50% risk of progression within 2 years should be the current goal of stratification because these are the patients most likely to have an underlying malignant transformation, and have shown the maximum benefit with early intervention in clinical trials. Multiple risk stratification models have been proposed [36-41]. To simplify these approaches, the Mayo 2018 model employs three variables: serum free light chain ratio >20, serum M-protein level >2gm/dL, and bone marrow clonal plasma cells >20%. Also called 20-2-20 criteria, the presence of 2 or 3 of these factors is able to identify patients as high-risk SMM with a median time to progression to multiple myeloma of approximately 2 years [42]. These patients should be handled like newly diagnosed high-risk SMM and qualify for clinical trials or early intervention. For all other patients considered low-risk by 20-2-20 criteria, observation remains standard of care. They should be monitored every 3–4 months including serum protein electrophoresis, serum FLC levels, complete blood count, serum calcium, and serum creatinine. If no progression occurs, the follow-up interval can be reduced to once every 6 months after the first 5 years [43]. Since low-risk SMM patients with 20% or greater bone marrow involvement have >90% risk of progression within 2 years, treatment should be considered if these patients develop an evolving change in monoclonal protein level plus an evolving change in hemoglobin [44]. For patients with diffuse infiltration, solitary focal lesion, or equivocal lesions on MRI scan, follow-up radiographic examination in 3–6 months is recommended [45]. If low-risk patients develop criteria for high-risk SMM during follow-up, early intervention similar to high-risk SMM should be considered.

If patients are ultimately diagnosed with high-risk SMM, therapy should be initiated. While early studies with alkylating agents found no significant benefit, a randomized trial comparing thalidomide plus zoledronic acid versus zoledronic acid alone showed some promise. However, neither regimen showed a significant difference in time to end organ damage [46,47]. Also, long-term side effects of thalidomide make it unsuitable for extended treatment. Two randomized trials used lenalidomide and dexamethasone (Rd) in high-risk SMM and found both time to progression to MM and overall survival to be significantly longer when compared to observation alone [48,49]. In addition, lenalidomide as single agent has been shown to prolong time to symptomatic MM [50]. Both approaches demonstrated a marked 90% reduction in time to end-organ damage.

Based on these trials, therapy with lenalidomide as single agent or Rd for two years should be discussed with newly diagnosed high-risk SMM patients. Besides, referral to a centre and enrollment in a clinical trial assessing early therapy or even intensive therapy with curative intent is recommended [51]. To chose between lenalidomide or Rd, patients' age, comorbidities, and tolerance to dexamethasone should be taken into account. Also, peripheral blood stem cells should be collected for cryopreservation after approximately 4–6 cycles of therapy [52,53].

To Summarize, MGUS and SMM are premalignant conditions that precede MM and other plasma cell dyscrasias. Although the majority of patients will never develop an aggressive malignancy, accurate risk stratification at diagnosis is indispensable in order to determine correct counseling and subsequent monitoring. The benefits of screening at risk people are still being debated; however, newer data suggests that active screening of MGUS patients could identify a higher number of patients at risk of progression. With the data currently available, treatment for MGUS is not indicated. Treatment of high-risk SMM with lenalidomide plus/minus dexamethasone should be discussed with the patient, taking into account all risk factors and possible side effects, and the patient should be referred to a centre to consider enrollment in a clinical trial.

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