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Plasma Cell Dyscrasias

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Part I
Monoclonal Gammopathy of Undetermined Significance and Smoldering Myeloma

MGUS and Smoldering Multiple Myeloma: Diagnosis and Epidemiology

María-Victoria Mateos and Ola Landgren

Abstract

Monoclonal gammopathy of undetermined significance (MHUS) is characterized by the presence of a serum M-protein less than 3 g/dL, less than 10 % clonal plasma cells in the bone marrow, and the absence of myeloma-defining event. Smoldering multiple myeloma (SMM) is an asymptomatic disorder characterized by the presence of ≥3 g/dL serum M-protein and/or 10–60 % bone marrow plasma cell infiltration with no myeloma-defining event. The risk of progression to multiple myeloma (MM) requiring therapy varies greatly for individual patients, but it is uniform and 1 % per year for MGUS, while higher (10 % per year) and not uniform for SMM patients. The definition of MM was recently revisited patients previously labeled as SMM with a very high risk of progression (80–90 % at 2 years) were included in the updated definition of MM requiring therapy. The standard of care is observation for MGUS patients and although this also applies for SMM, a recent randomized trial targeting high-risk SMM showed that early intervention was associated with better progression-free and overall survival. Biomarkers have become an integrated part of diagnostic criteria for MM requiring therapy, as well as clinical risk stratification of patients with SMM. This paper reviews and discusses clinical implications for MGUS and SMM patients.

Keywords

Multiple myeloma requiring therapy · Monoclonal gammopathy of undetermined significance · Smoldering myeloma

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1 Introduction

In 1978, Monoclonal gammopathy of undetermined significance (MGUS) was described by Kyle and Greipp and 2 years later, based on a series of six patients who met the criteria for multiple myeloma (MM) but whose disease did not have an aggressive course, the same authors coined the term smoldering multiple myeloma (SMM) [1]. In 2014, the International Myeloma Working Group (IMWG) updated the definition of multiple myeloma (MM) which in turn impacted the definition of both MGUS and SMM [2]. MGUS diagnosis requires the presence of <3 g/dL serum M-protein and <10 % bone marrow plasma cells with no hypercalcemia, renal failure, anemia, and bone lesions that can be attributed to the underlying plasma cell disorder. Indeed, SMM is now defined as a plasma cell disorder characterized by the presence of one or both of the features of ≥3 g/dL serum M-protein and 10–60 % bone marrow plasma cells (BMPCs), but with no evidence of myeloma-related symptomatology (hypercalcemia, renal insufficiency, anemia or bone lesions (CRAB)) or any other myeloma-defining event (MDE). According to this recent update, the definition of MM includes patients with BMPCs of 60 % or more, serum free light-chain (FLC) levels of ≥100, and those with two or more focal lesions of the skeleton as revealed by magnetic resonance imaging (MRI). Thus, the definition of MM requiring therapy has changed from symptoms to biomarkers. Kristinsson et al., through the Swedish Myeloma Registry, recently reported that 14 % of patients diagnosed with multiple myeloma indeed SMM, and, using the world population as a reference, estimated the age-standardized incidence of SMM to be 0.44 cases per 100,000 people [3]. The incidence of MGUS is higher than SMM and is present in roughly 3–4 % of the population over the age of 50 years [4].

2 Differential Diagnosis with Other Entities

Based on current diagnostic criteria, SMM is distinguished from monoclonal gammopathy of undetermined significance (MGUS) and MM requiring therapy (Table 1). Specifically, MGUS is characterized by a serum M-protein concentration of less than 3 g/dL, less than 10 % plasma cell infiltration in the bone marrow, and absence of CRAB criteria and absence of MDE [2]. Furthermore, MM requiring therapy is defined as follows: presence of one or more of the CRAB criteria and/or one of the MDE, in conjunction with 10 % or more clonal BMPC infiltration or biopsy-proven bony or extramedullary plasmacytoma. As per the criteria, presence of end-organ damage (i.e., CRAB criteria) needs to be correctly evaluated to distinguish myeloma-related symptomatology from some signs or symptoms that could otherwise be attributed to comorbidities or concomitant diseases [5].

Table 1 Differential diagnosis of MGUS, SMM and MM requiring therapy

Feature	MGUS	SMM	MM requiring therapy
Serum M-protein	<3 g/dL and	≥3 g/dL and/or	–
Clonal BMPC infiltration	<10 %	10–60 %	≥10 % or biopsy-proven plasmacytoma
Symptomatology	Absence of MDE*	Absence of MDE*	Presence of MDE*

*MDE includes (1) hypercalcemia: serum calcium > 0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL); (2) renal insufficiency: serum creatinine >177 μmol/L (2 mg/dL) or creatinine clearance <40 ml/min; (3) anemia: hemoglobin value of >2 g/dL below the lower normal limit, or a hemoglobin value <10 g/dL; (4) bone lesions: one or more osteolytic lesion revealed by skeletal radiography, CT, or PET-CT or the presence of any one or more of the following biomarkers of malignancy: clonal bone marrow plasma cell percentage ≥60 %; involved/uninvolved serum free-light chain ratio ≥100; >1 focal lesions revealed by MRI studies

3 Diagnostic Work-up

Initial investigation of a patient with suspected MGUS or SMM should include the tests shown in Table 2, which are coincidental with those used for a correct diagnosis of MM requiring therapy [6]. As far as SMM is concerned, due to the

Table 2 Work-up for newly diagnosed MGUS and SMM patients

• Medical history and physical examination
• Hemogram
• Biochemical studies, including of creatinine and calcium levels; Beta2-microglobulin, LDH and albumin
• Protein studies –Total serum protein and serum electrophoresis (serum M-protein) –24-h urine sample protein electrophoresis (urine M-protein) –Serum and urine immunofixation • Serum free light-chain measurement (sFLC ratio)
• Bone marrow aspirate ± biopsy: infiltration by clonal plasma cells, flow cytometry and fluorescence in situ hybridization analysis*
• Skeletal survey, CT, or PET-CT*
• MRI of thoracic and lumbar spine and pelvis; ideally, whole-body MRI (only for SMM)

FLC free light chain; *CT* computed tomography; *PET-CT* ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT; *MRI* magnetic resonance imaging
*These assessments can be deferred in patient with low-risk MGUS (IgG type, monoclonal protein <1.5 g/dL, normal free light-chain ratio)

updated IMWG criteria for the diagnosis of MM, there are some specific assessments to which physicians have to pay attention in order to make correct diagnosis.

(1) With respect to the evaluation of bone disease, the IMWG recommends that—in addition to a conventional skeletal survey—^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) and/or low-dose whole-body CT shall be conducted to rule our bone and/or bone marrow involvement. Specifically, the aim is to exclude presence of osteolytic bone lesions, currently defined by the presence of at least one lesion (≥5 mm) revealed by X-ray, CT, or PET-CT. In addition, whole-body MRI of the spine and pelvis (or, ideally, if available, whole-body MRI) is a required component of the initial work-up. It provides detailed information about bone marrow involvement and identifies potential focal lesions which have been found to predict a more rapid progression to MM requiring therapy. In 2010, Hillengass et al. reported that the presence of two or more focal lesions in the skeleton by whole-body MRI was associated with a significantly shorter median time to progression (TTP) to active disease of 13 months, compared with the period when no focal lesions were present [7]. Kastritis and colleagues replicated these observations based on a smaller group of patients who underwent spinal MRI and were followed up for a minimum of 2.5 years. In their study, the median TTP to symptomatic disease was 14 months when more than one focal lesion was present [8]. Therefore, if two or more focal lesions are detected by MRI, based on the most recent IMWG criteria (REF), such a patient is defined as having MM requiring therapy.

(2) With respect to bone marrow infiltration, the Mayo Clinic group evaluated BMPC infiltration in a cohort of 651 patients and found that 21 (3.2 %) had an extreme infiltration (≥60 %) [9]. This group of patients had a median TTP to active disease of 7.7 months, with a 95 % risk of progression at 2 years. This finding was subsequently validated in a study of 96 patients with SMM, in whom a median TTP of 15 months was reported for the group of patients with this extreme infiltration. In a third study, six of 121 patients (5 %) with SMM were found to have 60 % or more BMPC, and all progressed to MM within 2 years [10]. Therefore, based on the most recent IMWG criteria (REF), if 60 % or more of clonal plasma cell infiltration is present either in bone marrow aspirate or biopsy, the diagnosis is MM requiring therapy. Additional assessments, for example, by flow cytometry or by identifying cytogenetic abnormalities in SMM patients, are not required to confirm or rule out MM requiring therapy, but can help estimate the risk of progression from SMM to MM requiring therapy.

(3) With respect to the serum free light-chain (FLC) assay, Larsen et al. studied 586 patients with SMM to determine whether there was a threshold FLC ratio that predicted 85 % of progression risk at 2 years. They found a serum involved/uninvolved FLC ratio of at least 100 in 15 % of patients and a risk of progression to symptomatic disease of 72 % [11]. Similar results were obtained in a study by Kastritis and colleagues from the Greek Myeloma Group [12]. In their study of 96 SMM patients, 7 % had an involved/uninvolved FLC ratio of ≥100 and almost all progressed within 18 months. In a third study, the risk of progression within 2 years was 64 %. Consequently, if the involved/uninvolved ratio is ≥100,

and the involved FLC concentration is >10 mg/dL, based on the most recent IMWG criteria (REF), a patient fulfills the criteria for MM requiring therapy.

Once MM requiring therapy has been ruled out and a diagnosis of SMM has been made, considering the specific assessments mentioned above, the serum and urine M-component, hemoglobin, calcium, and creatinine levels should be reevaluated 2–3 months later to confirm the stability of these parameters. The subsequent follow-up involves the same evaluation but the frequency should be adapted on the basis of risk factors for progression to MM requiring therapy (see below).

Table 3 Smoldering MM: markers predicting progression to MM requiring therapy

Features for identifying high-risk MGUS patients
• Concentration of Serum M-protein: –M-protein of 2.5 g/dL ⟶ 49 % risk of progression at 20 years • Type of Serum M-protein: –Patients with IgM or IgA isotype, the risk is higher compared with IgG MGUS • Bone Marrow Plasma Cells: –>5 % of plasma cell bone marrow infiltration • Abnormal serum FLC ratio: –High risk of progression (Hazar ratio 3.5), independent of the concentration and type of serum M-protein.
Features for identifying high-risk SMM patients: 50 % at 2 years
• Tumor burden: –≥10 % clonal plasma cell bone marrow infiltration plus –≥3 g/dL of serum M-protein and –serum free light-chain ratio between 0.125 and 8 • Bence Jones proteinuria positive from 24-h urine sample • Peripheral blood circulating plasma cells >5 × 10^6/L
• Immunophenotyping characterization and immunoparesis: –≥ 95 % of aberrant plasma cells by flow within the plasma cell bone marrow compartment plus –immunoparesis (>25 % decrease in one or both uninvolved immunoglobulins relative to the lowest normal value)
• Cytogenetic abnormalities: –Presence of t(4;14) –Presence of del17p –Gains of 1q24 –Hyperdiploidy –Gene Expression Profiling risk score > −0.26
• Pattern of serum M-component evolution –Evolving type: if M-protein ≥ 3 g/dL, increase of at least 10 % within the first 6 months. If M-protein < 3 g/dL, annual increase of M-protein for 3 years –Increase in the M-protein to ≥3 g/dL over the 3 months since the previous determination
• Imaging assessments –MRI: Radiological progressive disease (MRI-PD) was defined as newly detected focal lesions (FLs) or increase in diameter of existing FL and a novel or progressive diffuse infiltration. –Positive PET/CT with no underlying osteolytic lesion

MRI magnetic resonance imaging; *PET-CT* ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT

4 Risk Factors Predicting Progression to MM Requiring Therapy

Patients diagnosed of MGUS have a low and uniform risk of progression to MM requiring therapy, 1 % per year [13]. However, most patients diagnosed with SMM will progress to MM requiring therapy and will need to start treatment. However, based on current criteria, SMM is not a uniform entity and once the diagnosis has been confirmed, the doctor should evaluate the risk of progression to MM requiring therapy with the aim to offer an appropriate, risk-based follow-up, and to optimize the management of the SMM patient. The average risk of progression from SMM to MM requiring therapy is about 10 % per year [14].

Several studies have proposed clinical predictors of progression from MGUS/SMM to MM requiring therapy. Although they are not exact by any means, such clinical markers are useful for physicians in that they provide a probability measure of progression (Table 3).

5 Management of MGUS and SMM Patients

Patients with MGUS should be tested again in 4–6 months since the suspicion of the diagnosis to exclude and evolving MM. The standard of care is not to treat unless MM or order plasma cell disorder is developed. The standard of care for the management of SMM patients has been observation until MM develops. However, several groups evaluated the role of early intervention in this group of patients using conventional and novel agents.

There have been different trials evaluating the role of early treatment with melphalan and prednisone (MP), or novel agents, such as thalidomide or even bisphosphonates.

None of these trials provided evidence favoring the early treatment of patients with SMM. However, they were conducted without considering the differences in the risk of progression to active disease, and while the high-risk subgroup of patients may have benefited, this could have been counterbalanced by the absence of benefit in low-risk patients. The Spanish Myeloma Group (GEM/Pethema) has conducted a phase III randomized trial in 119 SMM patients at high risk of progression to active disease (according to the Mayo and/or Spanish criteria) that compared early treatment with lenalidomide plus dexamethasone as induction followed by lenalidomide alone as maintenance versus observation. The primary end-point was TTP to symptomatic MM, and after a median follow-up of 40 months, the median TTP was significantly longer in patients in the early treatment group than in the observation arm (not reached vs. 21 months; hazard ratio, HR = 5.59; $p < 0.001$). Secondary end-points included response, OS and safety. The PR or better after induction was 82 %, including 14 % of cases of stringent complete response (sCR) plus CR, and after maintenance the sCR/CR rate increased to 26 %. The safety profile was acceptable and most of the adverse events reported

were grade 1 or 2. The OS analysis showed that the 3-year survival rate was also higher for the group of patients who received early treatment with lenalidomide-based therapy (94 vs. 80 %; HR = 3.24; $p = 0.03$) [15]. A recent update of this trial confirmed the efficacy of early treatment in terms of TTP (HR = 6.21; 95 % CI: 3.1–12.7, $p < 0.0001$) and the benefit to OS was even more evident with longer follow-up (HR = 4.35, 95 % CI: 1.5–13.0, $p = 0.008$) [16]. This study showed for the first time the potential for changing the treatment paradigm for high-risk SMM patients based on the efficacy of early treatment in terms of TTP to active disease and of OS. Moreover, several trials currently underway are focusing on high-risk SMM patients using novel agents.

6 Managing MGUS and SMM Patients in Clinical Practice

Patients with low-risk MGUS may be reevaluated every 2 years, whereas those with high-risk MGUS should be followed annually for life or until they develop an unrelated condition that severely limits life expectancy. At the time of the follow-up examination, a careful history and physical examination should be performed, looking for symptoms or signs of one of the malignant disorders known to evolve from MGUS. The serum and urine M-protein values should be measured, as well as the complete blood count, calcium, and creatinine. Patients should always be told to obtain medical evaluation promptly if clinical symptoms occur.

Concerning SMM, given the extensive background to this disease described above, the first step in clinical practice is to identify the risk of progression to active disease for each newly diagnosed SMM patient. A key question is which risk model is the best to use for the purpose of estimating the risk of progression from SMM to MM requiring therapy. The Mayo Clinic and Spanish models enable initial risk stratification of SMM and, in fact, both were validated in a prospective trial. However, new risk models are emerging that incorporate new clinical and biological features [10, 14, 17–22] (Table 4). The components of these models are not identical, and, importantly, they are all probability models and not markers reflective of defined biological mechanisms directly related to progression (Table 3).

SMM patients should be classified as follows:

(1) SMM patients at low risk of progression who are characterized by the absence of the aforementioned high-risk factors (using the validated Mayo and Spanish risk models), with an estimated probability of progression at 5 years of only 8 %. Patients in this group behave similarly to MGUS-like patients and should be followed annually.

(2) The second group includes SMM patients at intermediate risk of progression and they only display some of the aforementioned high-risk factors. They have a risk of progression at 5 years of 42 %, and they must be followed up every 6 months.