

REVIEW

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management

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Monoclonal gammopathy of undetermined significance (MGUS) was identified in 3.2% of 21 463 residents of Olmsted County, Minnesota, 50 years of age or older. The risk of progression to multiple myeloma, Waldenström's macroglobulinemia, AL amyloidosis or a lymphoproliferative disorder is approximately 1% per year. Low-risk MGUS is characterized by having an M protein <15 g/l, IgG type and a normal free light chain (FLC) ratio. Patients should be followed with serum protein electrophoresis at six months and, if stable, can be followed every 2–3 years or when symptoms suggestive of a plasma cell malignancy arise. Patients with intermediate and high-risk MGUS should be followed in 6 months and then annually for life. The risk of smoldering (asymptomatic) multiple myeloma (SMM) progressing to multiple myeloma or a related disorder is 10% per year for the first 5 years, 3% per year for the next 5 years and 1–2% per year for the next 10 years. Testing should be done 2–3 months after the initial recognition of SMM. If the results are stable, the patient should be followed every 4–6 months for 1 year and, if stable, every 6–12 months.

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Monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance (MGUS) is defined as a serum M protein <30 g/l, <10% clonal plasma

cells (PCs) in the bone marrow (BM) and, most importantly, the absence of end-organ damage that can be attributed to the PC proliferative disorder (Table 1). End-organ damage is characterized by CRAB (hypercalcemia, renal insufficiency, anemia, bone lesions) related to the PC proliferative disorder.¹

Prevalence of MGUS

MGUS was identified in 3.2% of 21 463 residents of Olmsted County, Minnesota, 50 years of age or older.² Age-adjusted rates were higher in men than in women (4.0 vs 2.7%). The prevalence of MGUS was 5.3% among persons 70 years of age or older and in 8.9% of men older than 85 years of age. The size of the M protein was <1.5 g/dl in 80% and ≥2 g/dl in only 4.5%.² The prevalence of MGUS in African Americans^{3,4} and Africans⁵ is approximately double that in Caucasians, whereas the prevalence in Japanese is lower than in Caucasians.⁶ The prevalence of MGUS in first degree relatives of patients with MGUS is increased suggesting a genetic factor.^{7,8} Only 21% of 70-year-old patients with MGUS have been recognized during routine clinical practice in a large population-based cohort.⁹ Fewer would likely be recognized outside Olmsted County because physicians might be less likely to order serum protein electrophoresis in everyday medical practice. At the time of its clinical recognition, the median duration of the patient's MGUS is estimated to be 11 years.

Outcome of MGUS

A cohort of 241 patients with MGUS was followed up to 39 years (median, 13.7 years). Twenty-seven percent ($n=64$) developed multiple myeloma (44), Waldenström's macroglobulinemia (7), primary AL amyloidosis (AL) (8), or a lymphoproliferative disorder (LP) (5). The interval from recognition of MGUS to diagnosis of multiple myeloma or a related disorder

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ranged from 1 to 32 years (median 10.4 years). The overall risk of progression was 1.5% per year.¹⁰ In a cohort of 1384 patients living in Southeastern Minnesota, 115 (8%) developed multiple myeloma ($n=75$), IgM lymphoma (19), AL amyloidosis (10), Waldenstrom's macroglobulinemia (7), chronic lymphocytic leukemia (3) or plasmacytoma (1). The relative risk of progression compared with the SEER (Surveillance, Epidemiology, and End Results) population from Iowa was 25.0, 2.4, 8.4, 46.0, 0.9 and 8.5-fold, respectively. The relative risk of progression was 7.3-fold in these patients when compared with the white population of the SEER data. The cumulative probability of progression was 12% at 10 years, 25% at 20 years and 30% at 25 years. The risk of progression was approximately 1% per year.¹¹

Predictors of risk of progression

Prediction of MGUS patients who will remain stable compared with those who progress is very difficult at the time of recognition of MGUS. However, the size of the M protein, type of M protein, number of BM PCs and the free light chain (FLC) ratio are helpful in identifying patients who are at a higher risk of progression. In addition, the physician should be aware that the presence of anemia, renal insufficiency or hypercalcemia may be unrelated to the presence of the M protein.

Size of M protein. The size of the M protein at the time of recognition of MGUS was the most important predictor of progression in 1384 patients with MGUS.¹¹ The risk of progression to multiple myeloma or a related disorder 20 years after recognition of MGUS was 49% for those with an M-protein value of 25 g/l, compared with only 14% for patients with an initial M-protein value of 5 g/l or less. The risk of progression with an M-protein value of 15 g/l was almost twice that of a patient with an M-protein value of 5 g/l. The risk of progression with an M protein of 25 g/l was 4.6 times that of a patient with a

5 g/l spike. Rosinol¹² emphasized that a progressive increase in size of the M protein during the first year of follow-up was the single most important risk factor for progression.

Type of immunoglobulin. Patients with IgM or IgA monoclonal protein had an increased risk of progression as compared with patients who had an IgG monoclonal protein in the 1384 patient cohort. Blade *et al.*¹³ also reported that patients with an IgA MGUS had a greater probability for progression to multiple myeloma.

Bone marrow plasma cells. Cesana *et al.*¹⁴ reported a series of 1104 patients with MGUS and found that those with more than 5% BM PCs had an increased risk of progression. In another series, the progression rate was 6.8% when the BM PCs were less than 10 and 37% for those in whom the PC level was 10–30%.¹⁵ At present, most would classify the patients with $\geq 10\%$ PCs as having smoldering multiple myeloma or symptomatic multiple myeloma.

Serum FLC ratio. One-third of 1148 patients with MGUS from Southeastern Minnesota had an abnormal FLC ratio at diagnosis. The risk of progression was significantly higher in patients with an abnormal FLC ratio than in those with a normal FLC ratio (hazard ratio 3.5). The FLC ratio was independent of the size and type of serum monoclonal protein.¹⁶

Rajkumar *et al.*¹⁶ developed a risk-stratification model for progression of MGUS. Patients with risk factors consisting of a serum M protein ≥ 15 g/l, IgA or IgM MGUS and an abnormal serum FLC ratio had a risk of progression at 20 years of 58%; compared with 37% when two risk factors were present; 21% when one risk factor was present; and only 5% when none of the risk factors were present (Table 2).

Flow cytometry and cytogenetics. In a study of 407 patients with MGUS and 93 with Smoldering (asymptomatic)

Table 1 Diagnostic criteria for plasma cell disorders

Disorder	Disease definition
Monoclonal gammopathy of undetermined significance	All three criteria must be met Serum monoclonal protein <3 gm/dl Clonal bone marrow plasma cells <10%, and Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions that can be attributed to the plasma cell proliferative disorder
Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Both criteria must be met Serum monoclonal protein (IgG or IgA) ≥ 3 gm/dl and/or clonal bone marrow plasma cells $\geq 10\%$, and Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder
Multiple myeloma	All three criteria must be met except as noted Clonal bone marrow plasma cells $\geq 10\%$ Presence of serum and/or urinary monoclonal protein (except in patients with non-secretory multiple myeloma), and Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically Hypercalcemia: serum calcium ≥ 11.5 mg/dl or Renal insufficiency: serum creatinine > 1.73 mmol/l Anemia: normochromic, normocytic with a hemoglobin value of > 2 g/dl below the lower limit of normal or a hemoglobin value < 10 g/dl Bone lesions: lytic lesions, severe osteopenia or pathological fractures

Abbreviations: MGUS, Monoclonal gammopathy of undetermined significance; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions.

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Table 2 Risk-stratification model to predict progression of monoclonal gammopathy of undetermined significance to myeloma or related disorders

Risk group	No. of patients	Relative risk	Absolute risk of progression at 20 years (%)	Absolute risk of progression at 20 years accounting for death as a competing risk (%)
Low-risk (serum M protein <1.5 gm/dl, IgG subtype, normal FLC ratio (0.26–1.65))	449	1	5	2
Low-intermediate-risk (any 1 factor abnormal)	420	5.4	21	10
High-intermediate-risk (any two factors abnormal)	226	10.1	37	18
High-risk (all three factors abnormal)	53	20.8	58	27

Abbreviation: MGUS, Monoclonal gammopathy of undetermined significance.

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multiple myeloma (SMM), Perez-Persona reported that a marked preponderance of aberrant PCs in the BM as assessed by flow cytometry showed a significantly higher risk of progression in both MGUS and multiple myeloma. The most important risk factors were the presence of $\geq 95\%$ aberrant PCs together with DNA aneuploidy. Using the two risk factors, they reported a progression-free survival of 2, 10 and 46% for the presence of none, one or two risk factors, respectively at 5 years in MGUS.¹⁷ The age, sex, presence of hepatosplenomegaly, values for hemoglobin, serum creatinine, serum albumin and presence or amount of a monoclonal urinary light chain are not predictors for progression. Although fluorescence *in situ* hybridization reveals almost the same number and type of abnormalities as in multiple myeloma, there is little evidence that this has a role in the progression of MGUS to multiple myeloma. The gene expression profile may be of benefit in predicting the risk of progression, but no convincing data exists at present.

Patient management

At first diagnosis, a complete history and physical examination should be done with emphasis on symptoms and findings that might suggest multiple myeloma or AL amyloidosis. A complete blood count, serum calcium and creatinine values and a qualitative test for urine protein should be performed. If proteinuria is found, electrophoresis and immunofixation is indicated. Serum protein electrophoresis should be repeated 3–6 months after recognition of MGUS to exclude multiple myeloma or Waldenstrom's macroglobulinemia because the monoclonal protein is usually recognized by chance.

Low-risk MGUS. If the serum monoclonal protein is <15 g/l, IgG type and the FLC ratio is normal, the risk of eventual progression to myeloma or related malignancy is low. In this setting, a baseline BM examination or skeletal radiography is not routinely indicated if the clinical evaluation, complete blood count, serum creatinine and calcium values suggest MGUS. On the other hand, a BM is required if the patient has unexplained anemia, renal insufficiency, hypercalcemia, or bone lesions. Patients should be followed with serum protein electrophoresis in 6 months, and if stable can be followed every 2–3 years or when symptoms suggestive of a PC malignancy arise.

Intermediate and high risk MGUS. If a patient with apparent MGUS has a serum monoclonal protein >15 g/l, IgA or IgM protein type, or an abnormal FLC ratio, a BM aspirate and

biopsy should be carried out at baseline to rule out underlying PC malignancy. As discussed earlier, a BM is always required if a patient with presumed MGUS has unexplained anemia, renal insufficiency, hypercalcemia, or bone lesions or a suspicion of AL amyloidosis. Both conventional cytogenetics and fluorescence *in situ* hybridization should be performed on the BM examination. If available, a PC labeling index and a search for circulating PCs in the peripheral blood using flow cytometry are useful.¹⁸ A computed tomographic scan of the abdomen should be done in the presence of an IgM monoclonal protein because asymptomatic retroperitoneal lymph nodes may be present. Lactate dehydrogenase, β -2-microglobulin, and C-reactive proteins should be determined if there is evidence of multiple myeloma or Waldenstrom's macroglobulinemia. If the results of these tests are satisfactory, patients should be followed with serum protein electrophoresis and a complete blood count in 6 months and then annually for life. Treatment is not indicated unless it is part of a clinical trial.¹⁹ Patients must contact their physician if there is any change in their clinical condition.

Smoldering (asymptomatic) multiple myeloma

Smoldering (asymptomatic) multiple myeloma requires the presence of a monoclonal protein level of 30 g/l or more or a proportion of clonal PCs in the BM of 10% or more but no end-organ damage.¹ It needs to be distinguished from MGUS because of a higher risk of progression to myeloma or related disorder; 10% per year for SMM versus 1% per year for MGUS.

Outcome

In a cohort of 276 patients fulfilling the criteria for SMM, 163 (59%) developed symptomatic multiple myeloma or AL amyloidosis during follow-up. The overall risk of progression was 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% per year for the last 10 years. The cumulative probability of progression to active multiple myeloma or AL amyloidosis was 51% at 5 years, 66% at 10 years, and 73% at 15 years. The median time to progression was 4.8 years.²⁰

The number of patients with progression to symptomatic multiple myeloma was 522 times the number of persons without SMM who would be expected to have active disease, whereas the risk of AL amyloidosis was increased by a factor of 50-fold. Ninety-seven percent of those who progressed developed symptomatic multiple myeloma.

Risk factors for progression

The size of the serum monoclonal protein and the number of PCs in the BM are the most important factors for progression. Sex, hemoglobin level, type of serum heavy chain, serum albumin value, presence and type of urinary light chain, reduction in levels of uninvolved immunoglobulins and involvement of the interfatty marrow space were not significant risk factors for progression. The FLC (free light chain) ratio is an independent additional risk factor for progression.²¹

On the basis of the size of the monoclonal protein and number of BM PCs, a risk-stratification model was developed.²⁰ If the patient had both $\geq 10\%$ PCs and ≥ 30 g/l of monoclonal protein, the probability of progression at 15 years was 87%; if the patient had $\geq 10\%$ PCs and < 30 g/l of monoclonal protein, the risk of progression was 70% at 15 years, whereas those patients with $< 10\%$ PCs and ≥ 30 g/l monoclonal protein had a progression risk of 39%. The median time to progression was 2 years, 8 years and 19 years, respectively in the above three groups. The type of serum heavy chain added significantly to the multivariate model containing the number of BM PCs and size of the serum M protein.

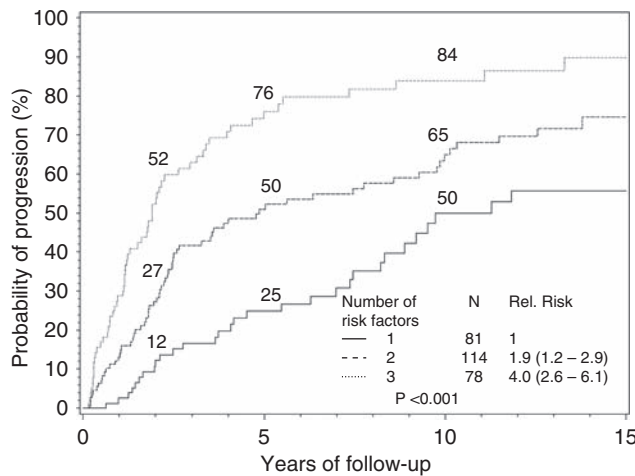


Figure 1 Risk stratification for smoldering multiple myeloma. The model incorporates three risk factors: abnormal FLC ratio, bone marrow plasma cells $\geq 10\%$ and serum M protein ≥ 3 g/dl. Patients with 1, 2 or 3 risk factors had 5-year progression rates of 25, 51 and 76%, respectively. Corresponding median times to progression are 10, 5.1 and 1.9 years, respectively.

Dispenzieri *et al.*²¹ found that the serum free light chain assay provides additional prognostic information. An abnormal FLC ratio (defined as ≤ 0.125 or ≥ 8) predicted for higher rates of progression, hazard ratio, 2.3; 95% CI, 1.6–3.2).²¹ A risk model was constructed, incorporating three risk factors: abnormal FLC ratio, BM PCs $\geq 10\%$, and serum M protein ≥ 3 g/dl. Patients with 1, 2 or 3 risk factors had 5-year progression rates of 25, 51 and 76%, respectively (Figure 1). Similar to what we have mentioned above for MGUS, the presence of $> 95\%$ aberrant PC from the total BM PC compartment detected by flow cytometry together with immunoparesis can discriminate three prognostic groups in SMM, with a progression risk of 5 years at 72, 46 and 4% if the patient has two, one or none of these risk factors.¹⁷

Others have found that the presence of occult bone lesions on magnetic resonance imaging (MRI) increases the risk of progression in patients otherwise defined as having SMM.²² In a recent study, Wang and colleagues²³ estimated risk of progression in 72 patients with SMM in whom an MRI of the spine was also performed. The median time to progression was significantly shorter with an abnormal MRI compared with normal MRI, 1.5 years versus 5 years.

Patient management

Serum protein electrophoresis, complete blood count, measurement of calcium and creatinine values and 24-h urine collection for electrophoresis and immunofixation should be performed at diagnosis and in 2–3 months after the initial recognition of SMM. A baseline BM biopsy and skeletal survey are mandatory. An MRI of the spine and pelvis is recommended because it can detect occult lesions and, if present, predict for a more rapid progression to symptomatic myeloma. If the results are stable, the studies should be repeated every 4–6 months for 1 year and, if stable, evaluation can be lengthened to every 6–12 months. A skeletal survey should be performed if there is evidence of progression in the above-mentioned routine studies.

Summary of IMWG recommendations for MGUS and SMM

Based on the discussion above, the summary recommendations that highlight the specific new recommendations by the IMWG panel are summarized in Table 3. As more data emerge we will reexamine these guidelines, particularly with regard to follow up

Table 3 Summary of new IMWG recommendations on the management of MGUS and SMM

New recommendation	Reason for change in recommendation
Definition of MGUS and SMM is based on proportion of clonal bone marrow plasma cells Patients with MGUS and SMM should be risk-stratified at diagnosis (see Table 2) to optimize counseling and follow up Follow up of MGUS is determined by the Risk-Stratification Model. Low-risk MGUS patients can be followed less frequently, either every 2–3 years or at time of progression. Preventive clinical trials need to be considered for patients with high risk smoldering myeloma	The disease definition has been updated to reflect that clonality assessment is important in classification New risk stratification models give greater precision in estimating risk of progression in MGUS and SMM. In fact, a low-risk MGUS group with a 2% actual lifetime risk of MGUS progression can be identified by these models. This change is to minimize frequent testing for MGUS progression in patients at low risk of progression, and to emphasize that these patients should be followed for other health problems that are far more likely to affect survival compared with MGUS progression Patients with smoldering myeloma with FLC ratio ≤ 0.125 or ≥ 8 plus $\geq 10\%$ plasma cells in the marrow are at high risk of progression in the first 2 years following recognition. These patients should be considered candidates for chemoprevention trials. However, off-study, observation is still the standard even in this group.

Abbreviations: MGUS, Monoclonal gammopathy of undetermined significance; SMM, smoldering (asymptomatic) multiple myeloma; IMWG, International Myeloma Working Group.

and prophylactic strategies. Understanding the biology and mechanisms of progression of MGUS/SMM to myeloma will provide major insights toward the goal of finding a cure for multiple myeloma.

Conflict of interest

The authors declare no conflict of interest.

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