



Monoclonal Gammopathy of Undetermined Significance (MGUS): Diagnosis, Predictors of Progression, and Monitoring

A Pocket Guide for the Clinician

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Recommendations in this guide are based on *Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: International Myeloma Working Group consensus perspectives risk factors for progression and guidelines for monitoring and management*¹ and additional sources.^{2,3,4,5,6}



Disease Definition

Monoclonal Gammopathy of Undetermined Significance (MGUS) is an asymptomatic condition that is included in a spectrum of monoclonal plasma cell disorders (dyscrasias). MGUS is characterized by a monoclonal protein (M protein) < 3 g/dL (30 g/L) in the serum and < 10% monoclonal plasma cells in the bone marrow and no evidence of end-organ damage ("CRAB": hypercalcemia, renal insufficiency, anemia or bone lesions), lymphoma, Waldenström macroglobulinemia, or light chain amyloidosis (AL). Smoldering multiple myeloma (SMM) also lies along this spectrum of plasma cell disorders, is also asymptomatic and is defined as having an M protein \geq 3 g/dL (30 g/L) and/or \geq 10% monoclonal plasma cells in the bone marrow and no CRAB features. Patients with high risk SMM may be candidates for clinical trials. It is important to follow patients with MGUS and SMM for disease progression.

Baseline Evaluation

A diagnosis of MGUS is relatively common, affecting 3.2% of the Caucasian population over the age of 50 years, and approximately 6% of the African American population. In patients with an M protein, the following baseline evaluation is recommended to either confirm a diagnosis of MGUS or rule out other more serious diagnoses:

Patient History

The following may suggest a diagnosis other than MGUS:

- Fatigue, easy bruising, or abnormal bleeding may indicate active multiple myeloma with cytopenias
- Bone pain or fractures may indicate active multiple myeloma
- Symptoms suggesting amyloidosis including weight loss, nephrotic syndrome with peripheral edema, or unexplained dyspnea (congestive heart failure)
- Neurologic symptoms, including sensory neuropathy associated with plasma cell dyscrasias (including amyloidosis, POEMS syndrome, multiple myeloma, or Waldenström macroglobulinemia) or symptoms of hyperviscosity
- Left upper quadrant discomfort or early satiety (splenomegaly can be a presenting sign of lymphoplasmacytic lymphoma)

Physical Exam

The following may indicate an underlying non-MGUS plasma cell dyscrasia or lymphoproliferative disease:

- Lymphadenopathy
- Hepatosplenomegaly
- Localized bone pain
- Periorbital purpura
- Macroglossia
- Peripheral neuropathy

Laboratory Evaluation

Table 1

Test	Comment
CBC	For a diagnosis of MGUS, results are within normal limits. Abnormal results may be indicative of an alternate diagnosis (see Table 3).
Calcium	
Creatinine	
LDH (lactate dehydrogenase)	
LFTs (liver function tests)	
Qualitative test for urine protein	May be diagnostic for a clonal plasma cell disorder. If the above qualitative test for urine protein is abnormal, check 24 hour urine collection for UPE and IFE.
Serum and urine protein electrophoresis (UPE) with immunofixation (IFE)	

Test	Comment
Quantitative (IgG, IgA and IgM) immunoglobulins	May be suggestive of a plasma cell disorder.
Serum immunoglobulin free light chains (including the ratio)	

Secondary Evaluation

Patients should undergo bone marrow aspiration and biopsy, including FISH and skeletal survey in the presence of an M-protein with any of the following:

- End-organ damage with "CRAB" features including hypercalcemia (Ca > 11 mg/dL or 2.75 mmol/L), renal insufficiency (creatinine > 2 mg/dL (177 μ mol/L) or creatinine clearance < 40 mL/min), anemia (hgb < 10 g/dL (100 g/L) or > 2 g/dL (20 g/L) below the lower limit of normal) and bone lesions (lytic lesions, severe osteopenia, or pathologic fracture).
- Non-IgG M-protein (IgA or IgM protein)
- IgG M-protein > 1.5 g/dL (15 g/L)
- Abnormal free light chain (FLC) ratio (FLC ratio < 0.26 or > 1.65)

Patients with an M-protein and suspected amyloidosis should undergo bone marrow aspirate and biopsy, and either a fat pad biopsy, rectal biopsy or biopsy of organ with suspected involvement by amyloidosis. The tissue should be stained with Congo Red and examined by mass spectroscopy or immunohistochemical stains. Decisions regarding which tissue to biopsy should take into consideration diagnostic yield and the invasiveness of the procedure.

Diagnostic Criteria

Plasma cell dyscrasias includes a spectrum of diseases.

Table 2

MGUS	Smoldering Multiple Myeloma (SMM) ²	Multiple Myeloma (MM)
M-protein < 3 g/dL (30 g/L)	M-protein \geq 3 g/dL (30 g/L)	End-organ disease (CRAB) including one or more osteolytic lesions on radiography, but more than one lesion is required if < 10% marrow plasma cells.
AND	AND/OR	From MRI imaging, there must be more than one lesion of > 5 mm in size.
Clonal bone marrow plasma cells < 10%	Urine monoclonal protein \geq 500 mg/24 hours	AND/OR
AND/OR	AND/OR	AND/OR
Urine monoclonal protein < 500 mg/24 hours	Clonal bone marrow plasma cells \geq 10%	Clonal bone marrow plasma cells > 60%
	Patients with SMM may require additional imaging including PET-CT, low-dose whole-body CT, or MRI of whole body or spine/pelvis	AND/OR
		An involved serum free light chain (kappa or lambda) > 100 mg/L with the ratio of the involved/uninvolved free light chains also > 100 mg/L

Key Predictors of Risk 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, Table 3 describes predictors associated with a higher risk of progression. To obtain a risk classification, one point is given for each risk factor to determine the cumulative risk as in Table 4.

Table 3

Risk factors for progression per Mayo criteria ³
M-protein > 1.5 g/dL (15 g/L)
Non-IgG isotype (IgA or IgM)
FLC Ratio < 0.26 or > 1.65

Classification of MGUS and Recommendations for Monitoring and Evaluation

Recommendations for monitoring and evaluation of a confirmed diagnoses of MGUS vary based on risk stratification. Table 4 lists the criteria that determine the likelihood of a patient with MGUS progressing to smoldering multiple myeloma or multiple myeloma.

Table 4

Associated Lab Values (from table 3)	Classification	Monitoring and Evaluation
No risk factors present	Low-risk MGUS (5% absolute risk of progression at 20 years) ³	Repeat serum protein electrophoresis in 6 months and every 2–3 years thereafter if stable No need for bone marrow biopsy or skeletal survey
1 risk factor present	Low intermediate-risk MGUS (21% absolute risk of progression at 20 years) ³	BM biopsy with FISH Consider CT abdomen if IgM monoclonal protein to exclude Waldenström Macroglobulinemia
2 risk factors present	High intermediate-risk MGUS (37% absolute risk of progression at 20 years) ³	LDH, β_2 microglobulin, CRP If all above are unremarkable, follow CBC serum protein electrophoresis, creatinine in 6 months, and then annually for life
3 risk factors present	High-risk MGUS (58% absolute risk of progression at 20 years) ³	

Factors Unrelated to Risk Progression

The following diagnostic factors are not useful for predicting risk of progression:

- Age
- Sex
- Presence of hepatosplenomegaly
- Hemoglobin
- Serum creatinine
- Serum albumin
- Presence or amount of a monoclonal urinary light chain

References

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