Monoclonal gammopathy of undetermined significance: Using risk stratification to guide follow-up

Varying combinations of 3 measurable factors determine a patient’s risk of progressing toward multiple myeloma and influence monitoring decisions. This review—and accompanying algorithm—can guide your approach.

**CASE** A 54-year-old man’s lab results following a routine annual examination reveal a level of IgM M-protein just under 1.5 g/dL. All other lab values, including free light chain (FLC) ratio and bone marrow exam, are normal. No clinical evidence of a related disorder is found. What is the risk that this patient’s condition could progress toward multiple myeloma, and how would you follow up?

The patient with a monoclonal gammopathy has an abnormal proliferation of monoclonal plasma cells that secrete an immunoglobulin, M-protein. This proliferation occurs most often in the bone marrow but can also be found in extra-medullary body tissue. The condition can begin insidiously, remain stable, or progress to frank malignancy causing bone and end-organ destruction. The major challenge is to separate stable, asymptomatic patients who require no treatment from patients with progressive, symptomatic myeloma who require immediate treatment.

An increased, measurable level of serum monoclonal immunoglobulins or FLCs is called monoclonal gammopathy of undetermined significance (MGUS) when there is <3 g/dL monoclonal protein in the serum, <10% monoclonal plasma cells in the bone marrow, and an absence of beta-cell proliferative disorders, lytic bone lesions, anemia, hypercalcemia, or renal insufficiency (**TABLE 1**). Serum and marrow measurements exceeding these values indicate progression of disease to a premalignancy stage. Continued proliferation of plasma cells in the bone marrow results in anemia and bone destruct-
Risk for MGUS progression increases markedly with a serum M-protein concentration ≥1.5 g/dL, a non-IgG isotype, or an abnormal serum FLC ratio (<0.26 or >1.65).

Detailed classification of MGUS: A roadmap for monitoring patients

Extensive epidemiologic and clinical studies have refined the classification of MGUS and related disorders (TABLES 2-4), providing physicians with guidance on how to monitor patients. There are 3 kinds of monoclonal gammopathies, each reflecting a particular type of immunoglobulin involvement—non-IgM, IgM, or light chain. Additionally, within each type of gammopathy, patient-specific characteristics determine 3 categories of clinical significance: premalignancy with low risk of progression (1%-2% per year); premalignancy with high risk of progression (10% per year); and malignancy.

Non-IgM MGUS with a high risk of progression is designated smoldering multiple myeloma (SMM) (TABLE 2). IgM MGUS with a high risk of progression is defined as smoldering Waldenström macroglobulinemia (SWM), with a predisposition to progress to Waldenström macroglobulinemia (WM) and, rarely, to IgM MM (TABLE 3).

More recently, it has been reported that approximately 20% of the cases of MM belong to a new entity called light-chain MM that features an absence of heavy chain (IgG, IgA, IgM, IgD, or IgE) secretion in serum. The premalignant precursor is light-chain MGUS (LC-MGUS). The criteria for LC-MGUS and idiopathic Bence Jones proteinuria are found in TABLE 4. Idiopathic Bence Jones proteinuria is equivalent to SMM and SWM due to its higher risk of progression (10%/year) to light-chain MM.

Prevalence of MGUS

In general, the prevalence of all types of MGUS increases with age and is affected by race, sex, family history, immunosuppression, and pesticide exposure. The Caucasian American population >50 years exhibits a prevalence of MGUS of approximately 3.2%; the African American population exhibits a significantly higher prevalence of 5.9% to 8.4%. Native Asians have a lower rate of MM, and, as expected, a lower MGUS prevalence than is seen in the Western population (Thailand ≈2.3%; Korea ≈3.3%; Japan ≈2.1%; China ≈0.8%). The overall prevalence of the 3 types of MGUS is 4.2% in Caucasians.

Distinguishing stable from progressing disease

The Mayo Clinic’s risk stratification model further specifies risk of disease progression based on 3 indicators: serum M-protein concentration, Ig isotype of M-protein, and serum FLC ratio. MGUS. A marked increase in risk for disease progression is associated with a serum M-protein concentration ≥1.5 g/dL, a non-IgG isotype, or an abnormal serum FLC ratio (<0.26 or >1.65, reflecting an increase in either the kappa or lambda light chain).

An MGUS patient exhibiting all 3 of these features has a 58% absolute risk of developing MM after 20 years of follow-up. A patient

---

**TABLE 1**

MGUS criteria established by IMWG and WHO

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-protein in serum &lt;3 g/dL</td>
<td></td>
</tr>
<tr>
<td>Bone marrow clonal plasma cells &lt;10%, and low level of plasma cell infiltration in a trephine biopsy</td>
<td></td>
</tr>
<tr>
<td>No evidence of B-cell proliferative disorder (MM, WM, AL)</td>
<td></td>
</tr>
<tr>
<td>No M-protein or only small amounts of monoclonal light chain in urine</td>
<td></td>
</tr>
<tr>
<td>Absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to the M-protein</td>
<td></td>
</tr>
</tbody>
</table>

AL, amyloid light-chain; IMWG, International Myeloma Working Group; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; WM, Waldenström macroglobulinemia; WHO, World Health Organization.
with 2 of the 3 abnormalities has a 37% risk of progressing to MM, and one who has just one abnormality has a 21% risk. In contrast, an MGUS patient who has an M-protein level <1.5 g/dL, an IgG isotype, and normal FLC range has only a 5% risk of progression to MM in the same 20 years.12

The Spanish Group risk stratification model13 is based on 2 risk factors: a high proportion of abnormal plasma cells (aPC) within the bone marrow plasma cell (BMPC) compartment (ie, ≥95% CD56+/CD19+); and an evolving subtype of the disease (defined as an increase in the level of serum M-protein by at least 10% during the first 6 months of follow-up, or a progressive and constant increase of the M-protein until overt MM develops). The 7-year cumulative probability of progression of MGUS to MM: 2% for patients with neither risk factor, 16% with one risk factor, and 72% with both risk factors.13

**SMM.** Classification of this progressive state is defined by a serum level of monoclonal protein (IgG, IgA, IgD, or IgE) ≥3 g/dL or a concentration of clonal bone marrow plasma cells ≥10%; and by an absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to a plasma cell proliferative disorder (TABLE 2).3 Both laboratory and clinical criteria must be met.

According to the Mayo Clinic risk stratification model, likelihood of progression reflects combinations of 3 factors: bone marrow plasmacytosis ≥10%, a serum M-protein level ≥3 g/dL, and a serum FLC ratio ≤0.125

**TABLE 2**

<table>
<thead>
<tr>
<th>Type of monoclonal gammopathy</th>
<th>Premalignancy with low risk of progression (1%-2% per year)</th>
<th>Premalignancy with high risk of progression (10% per year)</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>Non-IgM MGUS</td>
<td>SMM</td>
<td>MM</td>
</tr>
<tr>
<td></td>
<td>All 3 criteria must be met:</td>
<td>Both criteria must be met:</td>
<td>All 3 criteria must be met except as noted:</td>
</tr>
<tr>
<td></td>
<td>• Serum monoclonal protein &lt;3 g/dL</td>
<td>• Serum monoclonal protein (IgG or IgA) ≥3 g/dL or clonal BM plasma cells ≥10%</td>
<td>• Clonal BM plasma cells ≥10%</td>
</tr>
<tr>
<td></td>
<td>• Clonal BM plasma cells &lt;10%</td>
<td>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</td>
<td>• Presence of serum or urinary monoclonal protein (except in patients with true nonsecretory MM)</td>
</tr>
<tr>
<td></td>
<td>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</td>
<td>• Evidence of end-organ damage that can be attributed to the underlying PCPD, specifically:</td>
<td>• Evidence of end-organ damage that can be attributed to the underlying PCPD, specifically:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypercalcemia: serum calcium ≥11.5 mg/dL or</td>
<td>• Hypercalcemia: serum calcium ≥11.5 mg/dL or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal insufficiency: serum creatinine ≥2 mg/dL or</td>
<td>• Renal insufficiency: serum creatinine ≥2 mg/dL or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>estimated creatinine clearance &lt;40 mL/min</td>
<td>estimated creatinine clearance &lt;40 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anemia: normochromic, normocytic with hemoglobin &gt;2 g/dL below lower limit of normal or hemoglobin &lt;10 g/dL</td>
<td>• Anemia: normochromic, normocytic with hemoglobin &gt;2 g/dL below lower limit of normal or hemoglobin &lt;10 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bone lesions: lytic lesions or severe osteopenia</td>
<td>• Bone lesions: lytic lesions or severe osteopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>attributed to a PCPD</td>
<td>attributed to a PCPD</td>
</tr>
</tbody>
</table>

BM, bone marrow; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions; FISH, fluorescent in situ hybridization; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PCPD, plasma cell proliferative disorder; SMM, smoldering multiple myeloma.

or ≥8. Using this stratification scheme, the risk over 10 years of progressing from SMM to MM is 84% for those with all 3 risk factors, 65% with 2 factors, and 52% with one factor. As SMM is defined, there is no upper limit of bone marrow involvement. However, Rajkumar et al found that progression time was significantly shorter (<0.001) among patients with ≥60% bone marrow involvement, compared with those having <60% involvement.

The Spanish Group risk stratification model uses the same model applied to MGUS: a proportion of abnormal plasma cells in the BMPC compartment ≥95% CD56+/CD19-; and an evolving subtype of disease. The 3-year cumulative probability of progression of SMM to MM is 46% for those with both risk factors, 12% for those with one factor, and <1% for those with no risk factors.

**LC-MGUS**. The classification of LC-MGUS (TABLE 4) is primarily from a Mayo Clinic study and research on risk stratification is underway at 2 other institutions. False-positive results are possible in patients with renal and inflammatory disorders.

### Applying risk stratification to patient management

The current approach to a patient with clear-

<table>
<thead>
<tr>
<th>Type of monoclonal gammopathy</th>
<th>Premalignancy with low risk of progression (1%-2% per year)</th>
<th>Premalignancy with high risk of progression (10% per year)</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>All 3 criteria must be met:</td>
<td>All criteria must be met:</td>
<td>All criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>• Serum IgM monoclonal protein &lt;3 g/dL</td>
<td>• IgM monoclonal gammopathy (regardless of size of M-protein)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clonal BM lymphoplasmacytic cells &lt;10%</td>
<td>• ≥10% BM lymphoplasmacytic infiltration ≥10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</td>
<td>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</td>
<td></td>
</tr>
</tbody>
</table>

BM, bone marrow; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions; FISH, fluorescent in situ hybridization; MGUS, monoclonal gammopathy of undetermined significance; PCPD, plasma cell proliferative disorder; SWm, smoldering Waldenström macroglobulinemia; WM, Waldenström macroglobulinemia.

*Conventionally IgM MGUS is considered a subtype of MGUS. Unless otherwise specified, when the term MGUS is used in general, it includes IgM MGUS.

ly defined MGUS is a prudent “watch and wait” strategy that specifies monitoring details based on risk category (ALGORITHM).1,18

**MGUS.** In the low-risk MGUS group (IgG subtype, M-protein <1.5 g/dL, and normal FLC ratio)3 there is no need for bone marrow examination or skeletal radiography. Repeat the serum protein electrophoresis (SPE) in 6 months, and if there is no significant elevation of M-protein, repeat the SPE every 2 to 3 years.1,19,20 However, if other findings are suggestive of plasma cell malignancy (anemia, renal insufficiency, hypercalcemia, or bone lesions), bone marrow examination and computed tomographic (CT) scan are advised. Further evaluation of an incidental detection of MGUS is also important since it is occasionally associated with bone diseases,21 arterial and venous thrombosis,22 and an increased risk (P<.05) of developing bacterial (pneumonia, osteomyelitis, septicemia, pyelonephritis, cellulitis, endocarditis, and meningitis) and viral (influenza and herpes zoster) infections.23

Patients in the intermediate- and high-risk MGUS groups with serum monoclonal protein ≥1.5 g/dL, IgA or IgM subtype or an abnormal FLC ratio should undergo tests for CRAB and have bone marrow aspirate and biopsy with cytogenetics, flow cytometry, and fluorescence in situ hybridization (FISH). Patients with IgM MGUS should also undergo a CT scan of the abdomen to rule out the presence of asymptomatic retroperitoneal lymph nodes.1,19 If the BM examination and CT scan yield negative results, repeat SPE and complete blood count (CBC) after 6 months and annually thereafter for life. IgD or IgE MGUS is rare, and patients exhibit a progression similar to the 20-year risk seen with MGUS generally.

**SMM.** Given the increased risk of progression from SMM to MM compared with MGUS (all risk groups), the 2010 International Myeloma Working Group (IMWG) has suggested monitoring SMM patients more frequently—ie, SPE every 2 to 3 months in

### TABLE 4

<table>
<thead>
<tr>
<th>Type of monoclonal gammopathy</th>
<th>Premalignancy with low risk of progression (1%-2% per year)</th>
<th>Premalignancy with high risk of progression (10% per year)</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light chain</td>
<td>Light-chain MGUS</td>
<td>Idiopathic Bence Jones proteinuria</td>
<td>Light-chain MM*</td>
</tr>
<tr>
<td></td>
<td>All criteria must be met:</td>
<td>All criteria must be met:</td>
<td>Same as MM except no evidence of immunoglobulin heavy chain expression on immunofixation</td>
</tr>
<tr>
<td></td>
<td>• Abnormal FLC ratio (&lt;0.26 or &gt;1.65)</td>
<td>• Urinary monoclonal protein on urine protein electrophoresis ≥500 mg/24 hr and/or clonal BM plasma cells ≥10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased level of the appropriate involved light chain (increased k FLC in patients with ratio &gt;1.65 and increased λ FLC in patients with ratio &lt;0.26)</td>
<td>• No immunoglobulin heavy chain expression on immunofixation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No immunoglobulin heavy chain expression on immunofixation</td>
<td>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clonal BM plasma cells &lt;10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BM, bone marrow; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions; FLC, free light chain; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PCPD, plasma cell proliferative disorder.

*Conventionally, light chain MM is considered a subtype of MM. Unless otherwise specified, when the term MM is used in general, it includes light chain MM.

Work-up strategies for patients with a monoclonal band in the serum or urine

Algorithm

1. Consultation with an oncologist may be warranted if M-protein remains >1.5 g/dl or if there are suggestive
   clinical signs or abnormal test results: elevated creatinine, anemia, or hypercalcemia.
2. If M-protein is <1.5 g/dl, order Bm exam and repeat Spe in 6 months, then every 2-3 years thereafter, as long as M-protein remains <1.5 g/dl.
3. If M-protein is 1.5-3 g/dl, consider a referral to an oncologist.
4. If M-protein is ≥3 g/dl or the clone Bm plasma cell concentration ≥10%, order a Bm work-up and craB tests.

Suspect idiopathic Bence Jones proteinuria. Order a urinary monoclonal protein measurement every 6 months.

Suspect IgA or IgM subtype in addition to cBc and calcium and creatinine levels, order Bm exam.

If M-protein is <3 g/dl, the Bmpc concentration <10%, and the flc ratio is normal, Smm is likely.

Order an mri of the spine and pelvis. Are MRI findings normal?

If M-protein is ≥3 g/dl or the clone Bm plasma cell concentration ≥10%, order a Bm work-up and craB tests.

Suspect lc mGUS. Repeat the serum flc ratio measurement and renal function tests every 6 months.

With significant changes in serum or urinary values, repeat the Bm work-up or refer to an oncologist.

Suspect IgG subtype order cBc and calcium and creatinine levels. Are these results normal and is the M-protein level <1.5 g/dl and the flc ratio normal?

The patient has mGUS. Repeat Spe and cBc in 6 months and annually thereafter, as long as M-protein remains <3 g/dl.

For IgM disorder, add abdominal cT scan to reevaluations every 2-3 months for the first year; 4-6 months in following year; 6-12 months thereafter, as long as patient is clinically stable.

Refer to an oncologist.

The patient has IgA Smm or IgM SWm or Wm. Obtain an mri of the spine and pelvis. Are lytic lesions detected?

Suspect lc mGUS. Repeat the serum flc ratio measurement and renal function tests every 6 months.

No significant changes in serum or urinary values, do not refer to an oncologist.

Light-chain subtype abnormal flc ratio without heavy-chain expression on immunofixation. Order Bm work-up and flc levels.

If M-protein is >1.5 g/dl and the flc ratio is normal, consider Mw or MM. Order an mri of the spine and pelvis. Are MRI findings normal?

If M-protein is >1.5 g/dl and the flc ratio is abnormal, consider MM. Order a Bm work-up and spe.

If M-protein is >1.5 g/dl and the flc ratio is normal, consider MM. Order an mri of the spine and pelvis.

If M-protein is >1.5 g/dl and the flc ratio is abnormal, consider MM. Order a Bm work-up and spe.
the first year following diagnosis.¹ Repeat SPE in the second year every 4 to 6 months, and, if results are clinically stable, every 6 to 12 months thereafter. In addition to a baseline bone marrow examination (including cytogenetics, flow cytometry, and FISH studies), consider ordering magnetic resonance imaging of the spine and pelvis to detect occult lesions, as their presence predicts a more rapid progression to MM.²¹ During the course of the follow-up, evaluate any unexplained anemia or renal function impairment for its origin. A report of MGUS progression over more than a decade to SMM and then to MM illustrates prudent monitoring of a patient.²⁵

LC-MGUS. Once LC-MGUS is detected, first rule out AL-amyloidosis, light-chain deposition disease, or cast nephropathy. If no malignant state is present, repeat the FLC serum assay every 6 months with renal function tests. Idiopathic Bence Jones proteinuria and LC-MGUS have some overlap and both entities put patients at risk for developing MM or amyloidosis. It is not uncommon for MGUS to be accompanied by Bence Jones proteinuria.

In addition to a thorough history and physical examination, recommended follow-up for both of these entities includes CBC, creatinine, serum FLC, and 24-hour urine protein electrophoresis.⁶ With idiopathic Bence Jones proteinuria, a monoclonal protein evident on urine protein electrophoresis at >500 mg/24 hr must be followed up with tests for other signs of malignancy (CRAB) and BM examination to exclude the possibility of MM.⁶

**Treatment of MGUS to prevent progression**

Multiple myeloma is still an incurable disease. Since MGUS is a precursor of MM, attempts have been made to either slow its progression or eradicate it. Several independent intervention studies²⁶ for the precursor diseases MGUS and SMM have been conducted or are ongoing. Thus far, no conclusive preventive treatment has been found and the 2010 IMWG guidelines do not recommend preventive therapy for MGUS and SMM patients by means of any drug, unless it is a part of a clinical trial.¹

**CASE** The patient profiled at the start of this article has one abnormal risk factor (IgM isotype) and has a low risk of progression to MM. Management should follow the steps outlined in the ALGORITHM¹,² for low-risk IgM MGUS: repeat SPE, CBC, and CT scan in 6 months and annually thereafter. If any abnormality is observed, rule out the possibilities of IgM SWM, IgM WM, or rapid progression to MM, and consider referral to an oncologist.

**REFERENCES**


**CONTINUED**

**Likelihood of SMM progression varies with the combination of 3 factors:** bone marrow plasmacytosis ≥10%, a serum M-protein level ≥3 g/dL, and a serum FLC ratio ≤0.125 or ≥8.


