



# Why the Fuss Over MGUS

**Understanding the risk of progression  
to Multiple Myeloma**

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# What is MGUS?

- MGUS is a premalignant clonal plasma cell disorder
- It occurs in over 3% of the general population of people over 50
- Often identified as an incidental finding
- Wide variety of symptoms may provoke testing: peripheral neuropathy, hemolytic anemia, hypercalcemia or elevated sedimentation rate

Rajkumar, Vincent S. Clinical Course and Management of Monoclonal Gammopathy of Uncertain Significance. In: UpToDate, Post, TW (Editor), UpToDate, Waltham, MA 2019

# What is MGUS?

MGUS is defined by the presence of a serum monoclonal protein (M-protein), at a concentration <3 g/dL, bone marrow with <10 percent monoclonal plasma cells (if performed), and absence of end-organ damage (lytic bone lesions, anemia, hypercalcemia, renal insufficiency) related to the proliferative process

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, Rajkumar SV, Lancet Oncol. 2014;15(12):e538. Epub 2014 Oct 26

# MGUS Sub-types

- Non-IgM MGUS (IgG, IgA, IgD)
  - Most common form
  - Only a minority will progress to MM
  - Even fewer will progress to amyloidosis
- IgM MGUS
  - Can progress to Waldenstrom's macroglobulinemia
  - Can progress to NHL
- Light Chain MGUS
  - Can progress to light chain deposition disease or light chain MM

Rajkumar, Vincent S. Clinical Course and Management of Monoclonal Gammopathy of Uncertain Significance. In: UpToDate, Post, TW (Editor), UpToDate, Waltham, MA 2019

# Risk of MGUS

Progression to Multiple Myeloma (MM):

One percent per year

# Things with < 1% chance of happening

- Getting struck by lightning
- Getting bitten by a shark
- Falling off a roller coaster
- Being attacked by a bear in Yellowstone Park
- Getting hit by orbital debris
- Dying from a venomous snake bite

<https://www.boston.com/news/national-news/2013/07/23/what-are-the-odds>

# Smoldering MGUS (SMM)

SMM differs from MM based on the lack of end-organ damage; it is distinguished from (MGUS) based on the size of the M protein and the percent plasma cells in the bone marrow

In SMM the M-component is  $> 3$  g/dl and plasma cells are 10-60% in bone marrow

Rajkumar, Vincent S. Smoldering Multiple Myeloma. In: UpToDate, Post, TW (Editor), UpToDate, Waltham, MA 2019

# Diagnosing MGUS

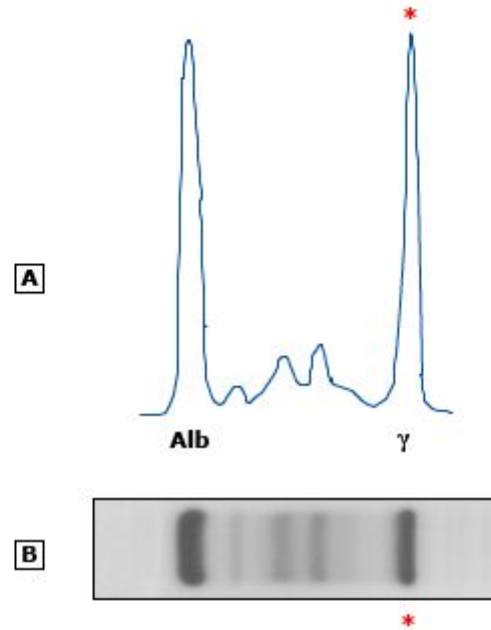
- Serum and urine electrophoresis and immunofixation
- CBC
- Serum Calcium
- Free Light Chain Assay
- Bone Marrow



# Serum Protein Electrophoresis (SPEP)

- This is usually the first test performed when an abnormal protein is suspected
- It identifies whether an abnormal protein is present but further testing (immunofixation) is required for further classification
- Electrophoresis can also be performed on urine to detect the presence of Bence-Jones proteinuria

## Monoclonal pattern on serum protein electrophoresis (SPEP)



(A) Densitometer tracing of these findings reveals a tall, narrow-based peak (asterisk) of gamma mobility and has been likened to a church spire. The monoclonal band has a densitometric appearance similar to that of albumin (alb) and a reduction in the normal polyclonal gamma band.

(B) A dense, localized band (asterisk) representing a monoclonal protein of gamma mobility is seen on SPEP on agarose gel (anode on left).

*Reproduced with permission from: Kyle RA, Rajkumar SV. Plasma cell disorders. In: Cecil textbook of medicine, 22nd ed, Goldman L, Ausiello DA (Eds), WB Saunders, Philadelphia 2004. p.1184. Copyright © 2004 Elsevier.*

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# Immunofixation

- Can reveal small quantities of M-protein undetectable via SPEP
- Can distinguish monoclonal protein from polyclonal protein
- Identifies specific heavy chain and light chain
  - Heavy chains: Gamma, Alpha, Mu, Delta and Epsilon
  - Light chains: Kappa and Lambda

# Urine Electrophoresis

- Same process for urine as for serum; UPEP identifies whether there is an abnormal protein (M-component), then Immunoelectrophoresis identifies if monoclonal and what type.
- The finding of an abnormal protein in the urine (light chains called Bence-Jones proteins) indicate something more than MGUS is present (SMM or MM, or amyloidosis)

# Free Light Chain Assay

- Assay is very sensitive and is used to determine concentrations of kappa and lambda light chains
- Abnormal ratio (either low or high) is a predictor of increased risk of progression to MM

# Factors that Increase Risk of Progression

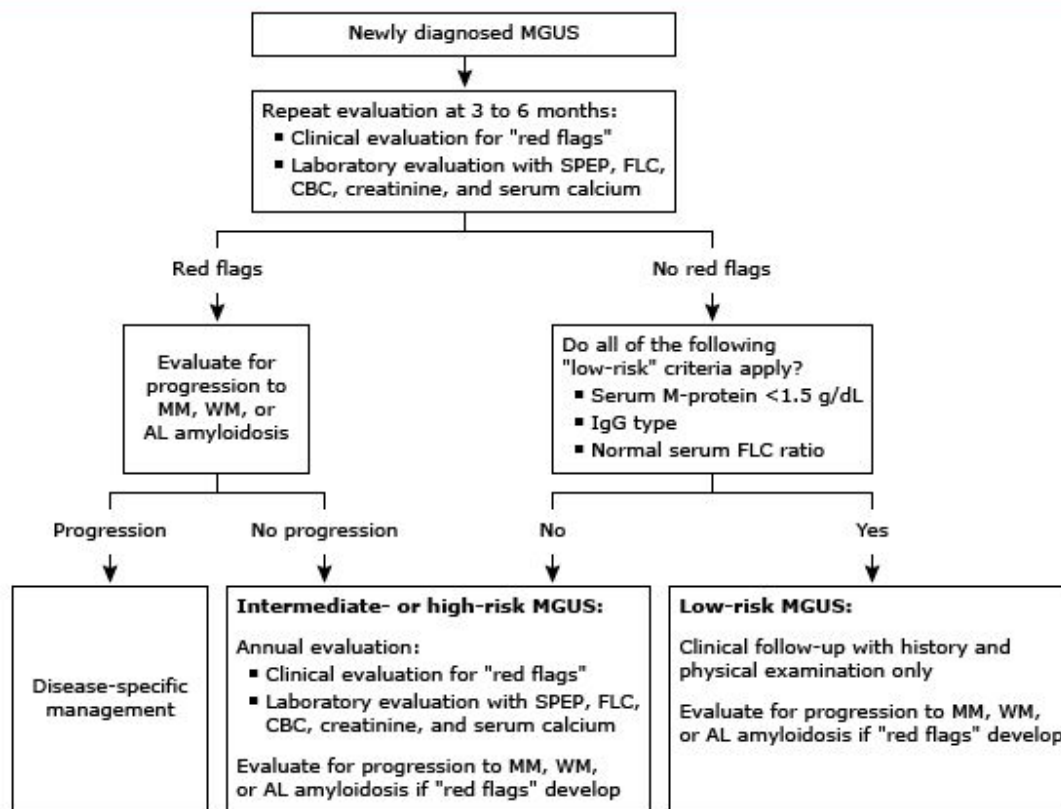
- Serum M-component  $\geq 1.5$  g/dl
- Non-IgG MGUS (IgA, IgD, IgM)
- Abnormal serum free light-chain ratio

# Risk of progression

- 3 risk factors (high risk MGUS) – 58 percent
- 2 risk factors (high-intermediate risk MGUS) – 37 percent
- 1 risk factor (low-intermediate risk MGUS) – 21 percent
- No risk factors (low risk MGUS) – 5 percent

Rajkumar SV, et al, Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance, Blood. 2005;106(3):812. Epub 2005 Apr 26

## Monoclonal gammopathy of undetermined significance: Monitoring for progression



Clinical "red flags" for progression:
▪ Bone pain
▪ Fatigue/generalized weakness
▪ Constitutional "B" symptoms (unintentional weight loss, fever, night sweats)
▪ Neurologic symptoms (neuropathy, headache, dizziness, loss of vision/hearing)
▪ Bleeding
▪ Symptoms suggestive of amyloidosis (macroglossia, nephrotic range proteinuria, restrictive cardiomyopathy, unexplained elevated NT-proBNP)
▪ Lymphadenopathy, hepatomegaly, or splenomegaly
Laboratory "red flags" for progression:
▪ Increase in serum M-protein level $\geq 50\%$ (provided absolute increase $\geq 0.5$ g/dL)
▪ Increase in serum FLC level $\geq 50\%$ (provided involved FLC level is at least 100 mg/L)
▪ Involved/uninvolved FLC ratio of 100 or more (provided involved FLC level is at least 100 mg/L)
▪ Serum M-protein $\geq 3$ g/dL
▪ Urine M-protein $\geq 500$ mg in 24 hours

MGUS: monoclonal gammopathy of undetermined significance; SPEP: serum protein electrophoresis; FLC: free light chain; CBC: complete blood count; MM: multiple myeloma; WM: Waldenström macroglobulinemia; AL amyloidosis: immunoglobulin light chain amyloidosis; M-protein: monoclonal protein; IgG: immunoglobulin G; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

Adapted from: Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. *Blood* 2018; 131:163.

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# Risk of progression

- Bone pain
- Fatigue/generalized weakness
- Constitutional "B" symptoms (unintentional weight loss, fever, night sweats)
- Neurologic symptoms (neuropathy, headache, dizziness, loss of vision/hearing)
- Bleeding
- Symptoms suggestive of amyloidosis (macroglossia, nephrotic range proteinuria, restrictive cardiomyopathy, unexplained elevated NT-proBNP or hepatomegaly)
- Lymphadenopathy, hepatomegaly, or splenomegaly
- Anemia, elevated creatinine, hypercalcemia
- Increase in serum M-protein level  $\geq 50$  percent (provided absolute increase  $\geq 0.5$  g/dL) or serum M-protein  $\geq 3$  g/dL
- Increase in involved serum FLC level by  $\geq 50$  percent or involved/uninvolved FLC ratio  $\geq 100$  (provided involved FLC level is at least 100 mg/L)
- Urine M-protein  $\geq 500$  mg in 24 hours
- Rajkumar, Vincent S. Clinical Course and Management of Monoclonal Gammopathy of Uncertain Significance. In: UpToDate, Post, TW (Editor), UpToDate, Waltham, MA 2019

# Bone Marrow

Increasing percentage of bone marrow plasma cells may also be a predictor of progression but is not used in the model

Prognostic factors for malignant transformation in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma, Cesana C, J Clin Oncol. 2002;20(6):1625

In order to be considered MGUS plasma cells need to be < 10%

With improved diagnostic and prognostic tests bone marrow testing is seen less often than in past

# Beta 2 microglobulin

- Used in staging and survival prediction of Multiple Myeloma along with serum albumin, creatinine, platelet count and age

International staging system for multiple myeloma, Greipp PR, et al, J Clin Oncol. 2005;23(15):3412. Epub 2005 Apr 4.

- Not as useful for predicting MGUS progression to MM but levels are higher in 'smoldering MM' than in MGUS

# Something (relatively) New

- **Monoclonal Gammopathy of Clinical Significance**
  - **Meets criteria for MGUS but has evidence of end-organ damage**
  - **Requires rapid identification and treatment to prevent progressive damage (Chemotherapy)**

Fernand JP, Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications *Blood*. 2018;132(14):1478. Epub 2018 Jul 16

# Thank You

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