Work up of Monoclonal Gammopathy of Undetermined Significance (MGUS)

The road to success is always under construction.

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Disclosures/COI

- NONE

*What is a monoclonal gammopathy?

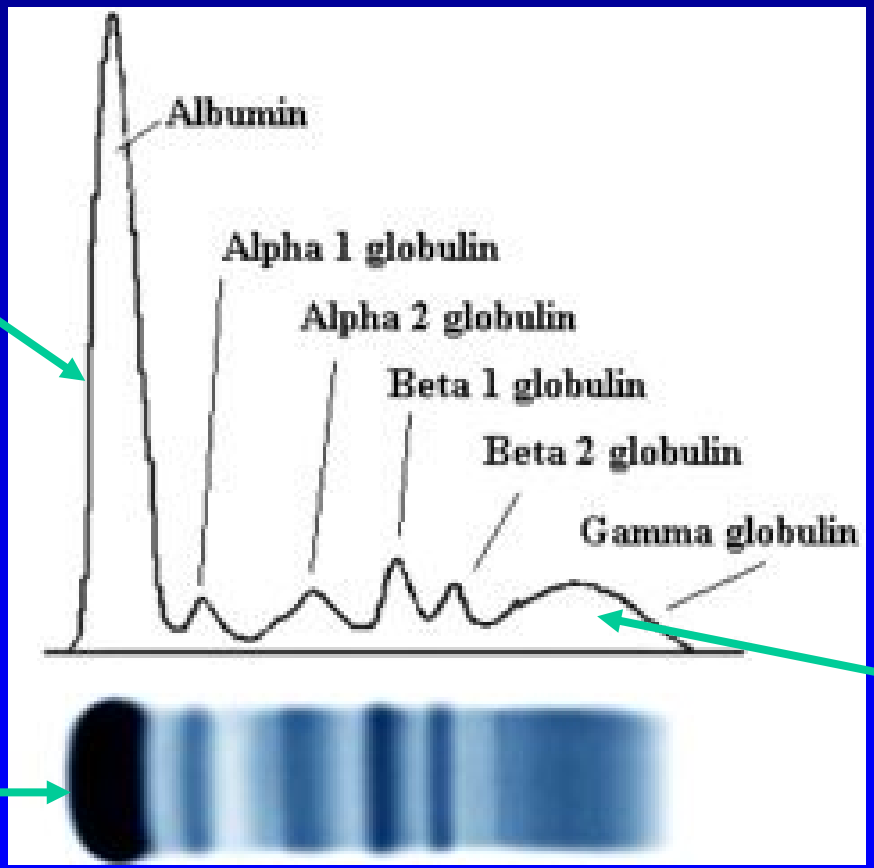
- The presence of an immunoglobulin molecule (IgG, IgA, IgM) in the serum or urine produced and secreted by a single clone of cells

Presenting Symptoms of MGUS

- None!
- By definition, MGUS is an asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder

SPEP-Protein Electrophoresis is gel electrophoresis of the serum

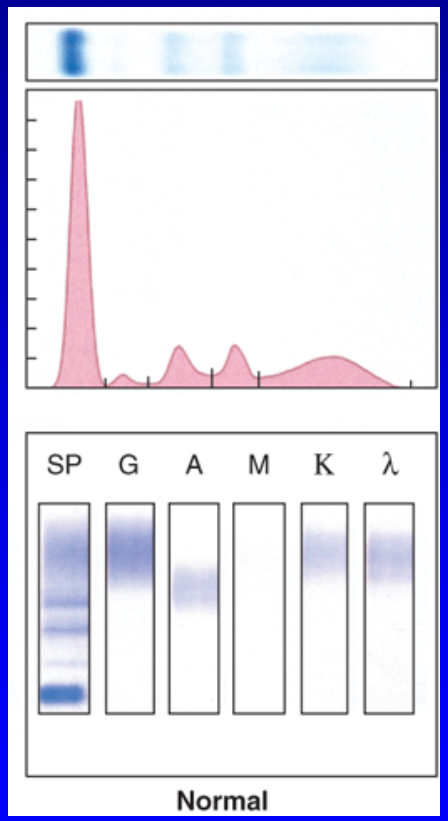
Densitometry is applied to the gel to quantify

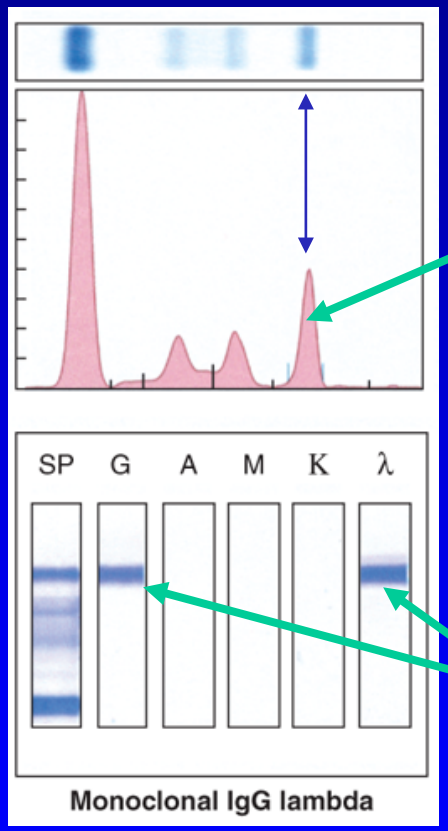


Protein gel

Antibodies typically migrate in the gamma region

Protein Electrophoresis and Immunofixation





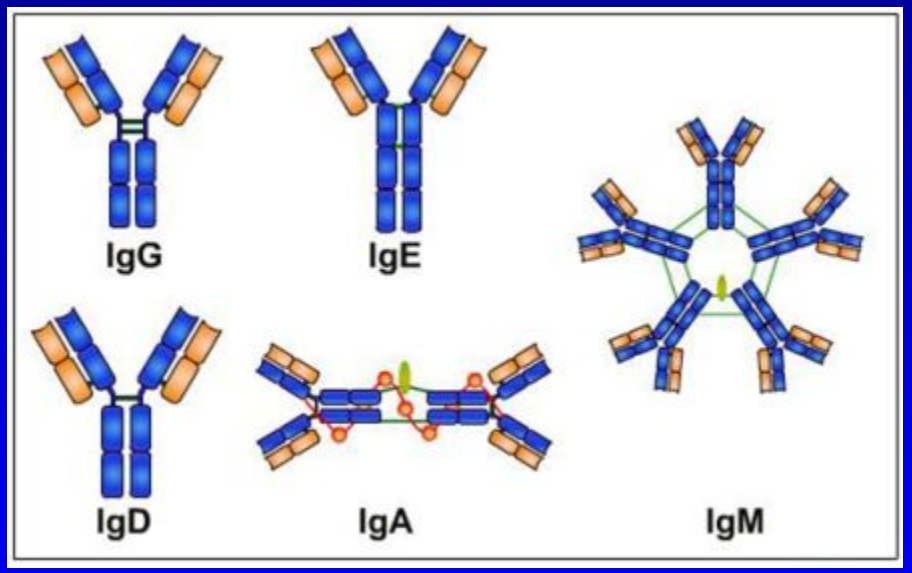
Monoclonal or M-spike

Immunofixation with anti-IgG, IgA, IgM, and anti Kappa and Lambda light chains identifies the monoclonal proteins

Citation: Chapter 107 Plasma Cell Disorders, Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. *Harrison's Principles of Internal Medicine, 20e;* 2018. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192018291 Accessed: October 20, 2020

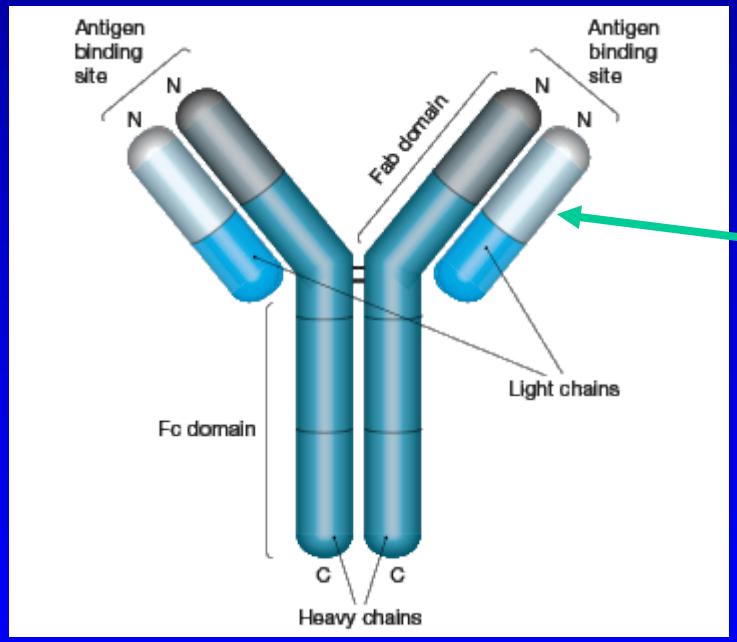
Distribution of Monoclonal Proteins

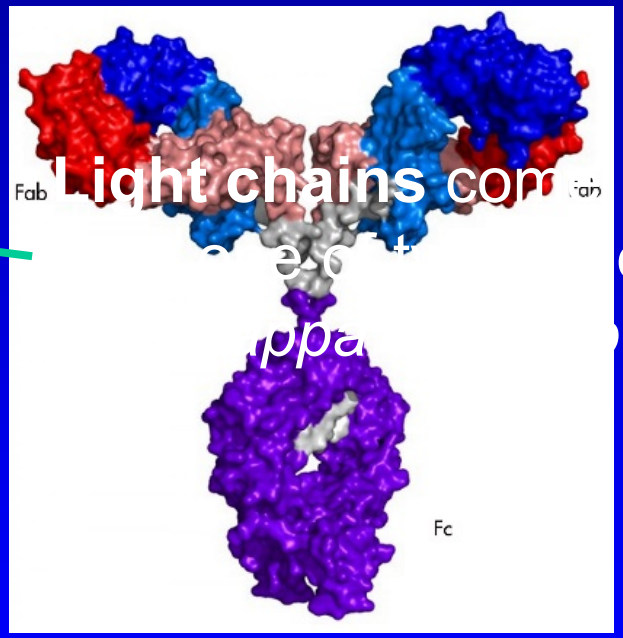
- IgG – 70 percent
- IgM – 15 percent
- IgA – 12 percent
- IgD – <1 percent
- Biclonal – 3 percent
- Kappa light chain – 61 percent
- Lambda light chain – 39 percent



N Engl J Med 2018;378:241-9

Antibodies are classified according to the source of the light chain





Heavy and light chain are normally made 1:1.4 The excess FLC is cleared and catabolized by the kidney

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Definition:

- Monoclonal spike < 3 g/dl
- <10% plasma cells in bone marrow
- Absence of end organ damage
  - Hypercalcemia
  - Renal insufficiency
  - Anemia
  - Lytic bone lesions

Presence of one of these factors defines Myeloma or Smoldering Myeloma

*Absence of end organ damage CRAB criteria

- No CRAB
  - C: Elevated Calcium (>11mg/dl)
  - R: Renal insufficiency (>2mg/dl or ClCr <40)
  - A: Anemia Hgb (<10 g/dl)
  - B: Lytic Bone lesions/severe osteopenia/fracture

Why is there a lot of MGUS?

- Most MGUS is identified when a monoclonal protein is detected as an incidental finding on SPEP ordered for workup of neuropathy, anemia, hypercalcemia, elevated ESR

Epidemiology

- The mean age at diagnosis is 70 years
- Less than 2 percent of patients are diagnosed before the age of 40

Prevalence off MGUS in Olmsted County, MN-*mostly Caucasians*

- ≥50 years of age was 3.2%
- ≥70 years of age was 5.3%
- ≥85 years of age was 7.5%
- Higher in men than women (4.0 versus 2.7 percent)

N Engl J Med. 2006;354(13):1362.

Incidence is higher in Blacks

- The prevalence of MGUS in Ghanaian men was twice that in white Minnesotan men[1]
- A VA study showed an age-adjusted prevalence ratio of 3.0 for MGUS in Blacks compared with whites[2]

[1]Mayo Clin Proc. 2007;82(12):1468.
[2]Blood. 2006;107(3):904. Epub 2005 Oct 6

Incidence is higher in relatives of persons with MGUS

- In Sweden, relatives of MGUS patients had increased risks for MGUS (RR 2.8)[1]
- In Olmsted County the risk of MGUS was increased among relatives of those with myeloma (RR 2.0) or MGUS (RR 3.3)[2]

[1]Blood. 2009;114(4):791
[2]Blood. 2009;114(4):785

*Workup of MGUS

Evaluate for end organ damage (CRAB)

- CBC, Calcium, Creatinine
- SPEP and immunofixation
- Free light chain assay
- Imaging of the bones (can be omitted in low risk MGUS)
- Bone Marrow biopsy (can be omitted in low risk MGUS)

*Three risk factors for progression:

- Serum M-protein level ≥1.5 g/dL
- Non-IgG MGUS (IgA, IgM, IgD MGUS)
- Abnormal free light chain (FLC) ratio
  - kappa to lambda <0.26 or >1.65

*Risk of MGUS progression over 20 years

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

Progression patterns

- IgG and IgA MGUS: progresses to myeloma
  - Presentation is CRAB dominated
- IgM MGUS progresses to Waldenström macroglobulinemia
  - Presentation is lymphoma like with “B” symptoms, anemia, splenomegaly, neurologic symptoms and symptoms of hyperviscosity

Survival of Patients with MGUS is measurably affected

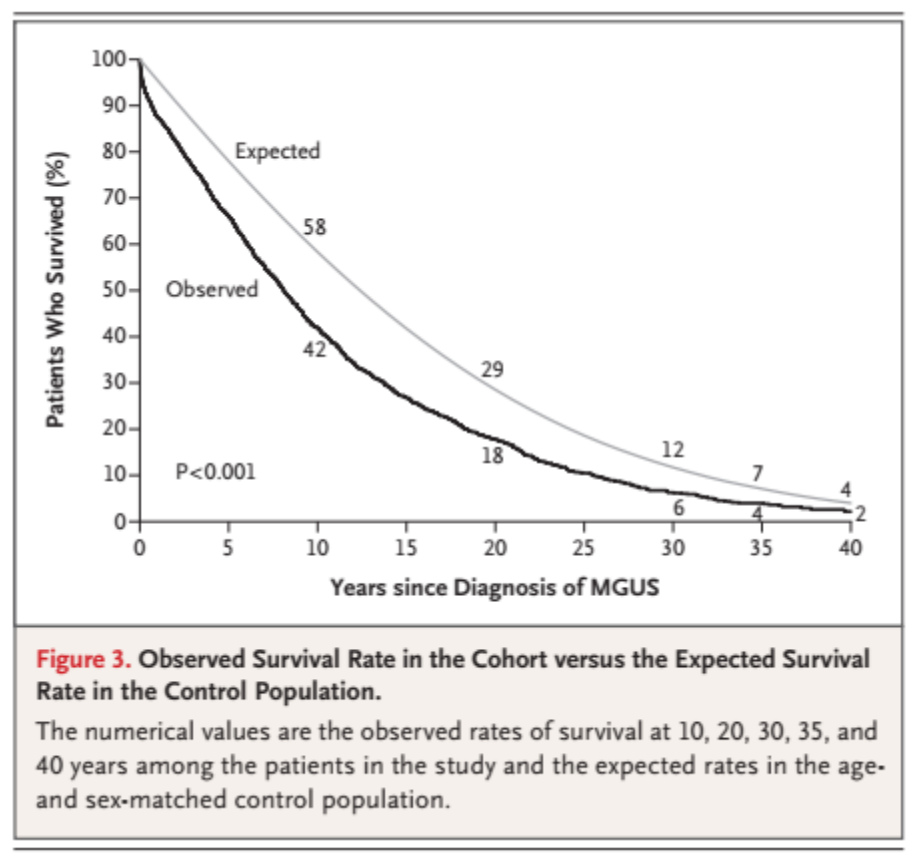


Figure 3. Observed Survival Rate in the Cohort versus the Expected Survival Rate in the Control Population.

The numerical values are the observed rates of survival at 10, 20, 30, 35, and 40 years among the patients in the study and the expected rates in the age- and sex-matched control population.

- Probability of progressing during a patient's lifetime is approximately 10 % due to competing causes
- There is an excess risk of dying from bacterial infections as well as heart, liver, and renal diseases (mechanism unclear)

N Engl J Med 2018;378:241-9
Leukemia. 2008;22(9):1651
Haematologica. 2009;94(12):1714

Bone imaging

- Can be omitted in the low risk group
- Required for anyone with risk factors or unexplained anemia, hypercalcemia, renal disease
- Recommended imaging:
  - Low dose noncontrast CT- sensitive, low cost
  - Whole body MRI- picks up marrow lesions
  - Whole body PET-most sensitive, costly
  - Skeletal survey- least sensitive, lowest cost

*Who to refer?

- Any non “low risk” patient
  - These patients need counseling about bone marrow biopsy
- Any patient without a clear explanation for anemia, renal dysfunction, hypercalcemia

Clinical Red Flags to watch for

- Bone pain
- Fatigue/generalized weakness
- Constitutional "B" symptoms (unintentional weight loss, fever, night sweats)
- Neurologic symptoms (neuropathy, headache, dizziness, loss of vision/hearing)
- Symptoms suggestive of amyloidosis (macroglossia, bleeding, proteinuria, restrictive cardiomyopathy)
- Lymphadenopathy, hepatomegaly, or splenomegaly

*Monitoring

- Low risk (0 risk factors)-clinical only
  - Follow up with PCP office
- Intermediate or high risk (1 or more risks)
  - Annual SPEP, FLC, CBC, creatinine, calcium
  - Follow up with oncologist

Monitoring

- The evolution from MGUS to Myeloma may be abrupt.
- Patients should obtain medical evaluation promptly if clinical symptoms occur
- Patients with MGUS are at increased risk of fracture.
  - Patients with MGUS should be evaluated for osteoporosis and treated as patients without MGUS.

Thank you

When you come to a fork in the road, take it.