

Case #1

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Patient History Part I

- 76 year-old man
 - 1997 diagnosed with MGUS (biclonal) during evaluation of (self-limited) anemia. Stable.
 - 2002 diagnosed with indolent CD30+ anaplastic large cell lymphoma, managed with topical steroids.
 - 2006 had MRI/CT for evaluation of hip pain. Incidentally found to have retroperitoneal and mesenteric lymphadenopathy. Biopsy. Dx low volume CLL/SLL (nl CBC); tx observation

Patient History Part II

- Fall 2011 developed dental abscess.
 - root canal, then dental implant
 - dental implant infected, then removed
 - osteomyelitis, treated with prolonged antibiotics
 - sinus infection
 - sinus surgery and more antibiotics

ENT follow-up note:

“On 12/23/11, he underwent removal of left concha bullous, anterior ethmoidectomy, and left maxillary antrostomy; he was given Cleocin-300 mg. At that time I obtained a culture, the results returning as staphylococcus aureus. I would have liked to start him on doxycycline-100 mg QD but the patient is reluctant to take yet another antibiotic and requests to see an infectious disease specialist.”

CBC, kidney,
liver, A1C 7.0
& immunoglobulins
are all stable

IgA is
somewhat low,
not stable.

11/7/2012

Seen in routine follow-up

“Worst year of my life.”

Normal physical exam.

CBC (11/7/12)

WBC	6.3
RBC	4.45
Hemoglobin	13.7
Hematocrit	40.5
MCV	91.0
Plt	220,000

WBC Differential

WBC	6.3
% lymphs	24
%mono	15 (H)
%eos	6
%PMN	55
%blast	0

Chemistries

CA	9.6
TBILI	1.0
Total Protein	6.9
Albumin	4.4
Globulin	2.5

<u>Total Protein</u>	<u>6.7 g/dl</u>	<u>6.0 - 8.0 g/dL</u>
<u>Albumin</u>	<u>3.80 g/dl</u>	<u>3.20 - 5.30 g/dL</u>
<u>Alpha 1</u>	<u>0.21 g/dl</u>	<u>0.10 - 0.40 g/dL</u>
<u>Alpha 2</u>	<u>0.82 g/dl</u>	<u>0.50 - 1.00 g/dL</u>
<u>Beta</u>	<u>0.78 g/dl</u>	<u>0.60 - 1.20 g/dL</u>
<u>Gamma</u>	<u>1.08 g/dl</u>	<u>0.80 - 1.70 g/dL</u>
<u>IgG</u>	<u>942 mg/dl</u>	<u>700 - 1600 mg/dL</u>
<u>IgA</u>	<u>32 mg/dl</u>	<u>70 - 400 mg/dL</u>
<u>IgM</u>	<u>259 mg/dl</u>	<u>40 - 230 mg/dL</u>
<u>Gamma M Spike 1</u>	<u>0.18 g/dl*</u>	<u>IgM Lambda paraprotein</u>
<u>Gamma M Spike 2</u>	<u>0.62 g/dl*</u>	<u>IgG Lambda paraprotein</u>

INTERPRETATION:

Protein Electrophoresis:

-Two M-spikes detected

Immunofixation:

-Biclonal gammopathy with IgG Lambda paraprotein (0.62g/dL) and IgM Lambda paraprotein (0.18g/dL).

<u>Total Protein</u>	<u>6.7 g/dl</u>	<u>6.0 - 8.0 g/dL</u>
<u>Albumin</u>	<u>3.80 g/dl</u>	<u>3.20 - 5.30 g/dL</u>
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1. Serum Protein Electrophoresis

<u>IgG</u>	<u>942 mg/dl</u>	<u>700 - 1600 mg/dL</u>
<u>IgA</u>	<u>32 mg/dl</u>	<u>70 - 400 mg/dL</u>
<u>IgM</u>	<u>259 mg/dl</u>	<u>40 - 230 mg/dL</u>

2. Quantitative Immune Globulins, (Nephelometry)

<u>Gamma M Spike 1</u>	<u>0.18 g/dl*</u>	<u>IgM Lambda paraprotein</u>
<u>Gamma M Spike 2</u>	<u>0.62 g/dl*</u>	<u>IgG Lambda paraprotein</u>

3. Immunofixation

INTERPRETATION:

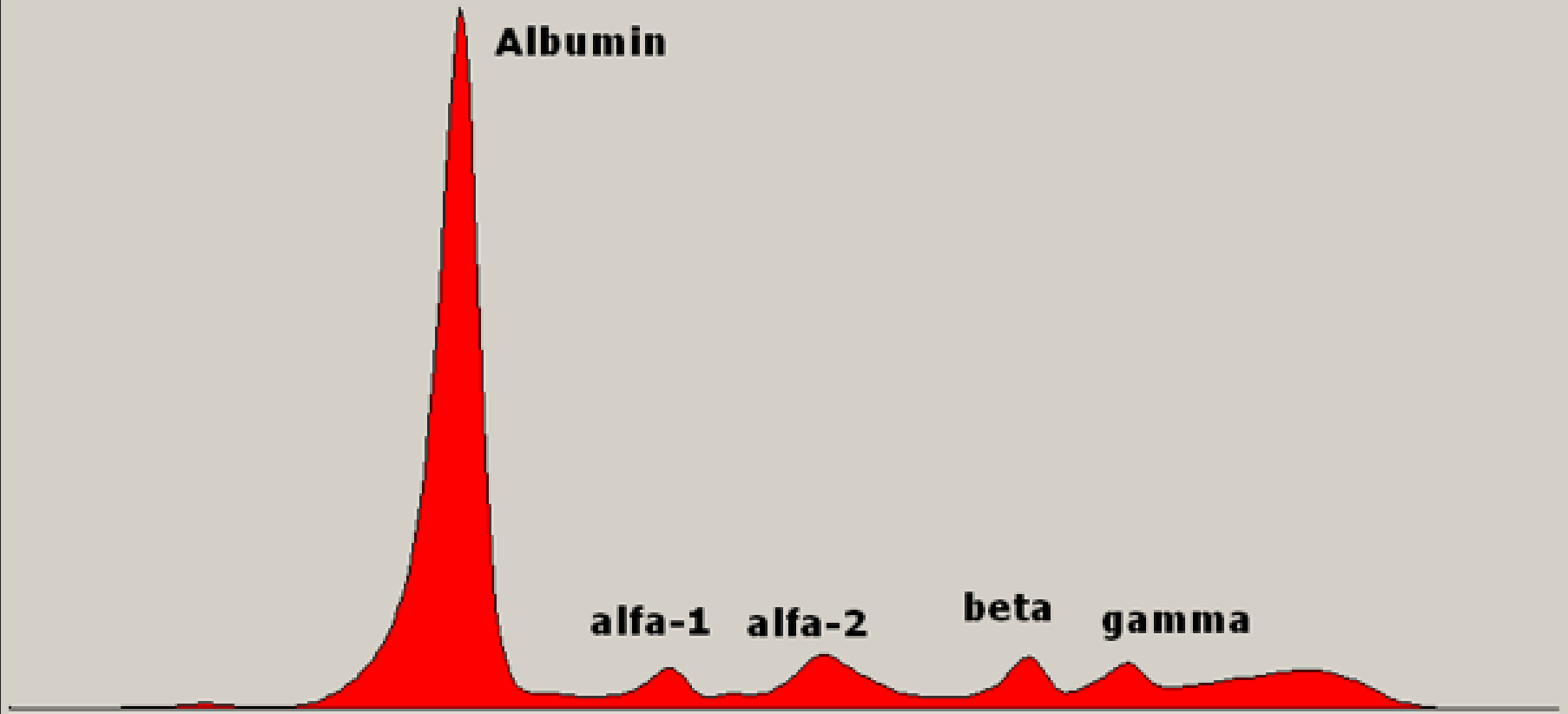
Protein Electrophoresis:

-Two M-spikes detected

Immunofixation:

-Biclonal gammopathy with IgG Lambda paraprotein (0.62g/dL) and IgM Lambda paraprotein (0.18g/dL).

1. Serum Protein Electrophoresis: separation of proteins based on charge and molecular weight



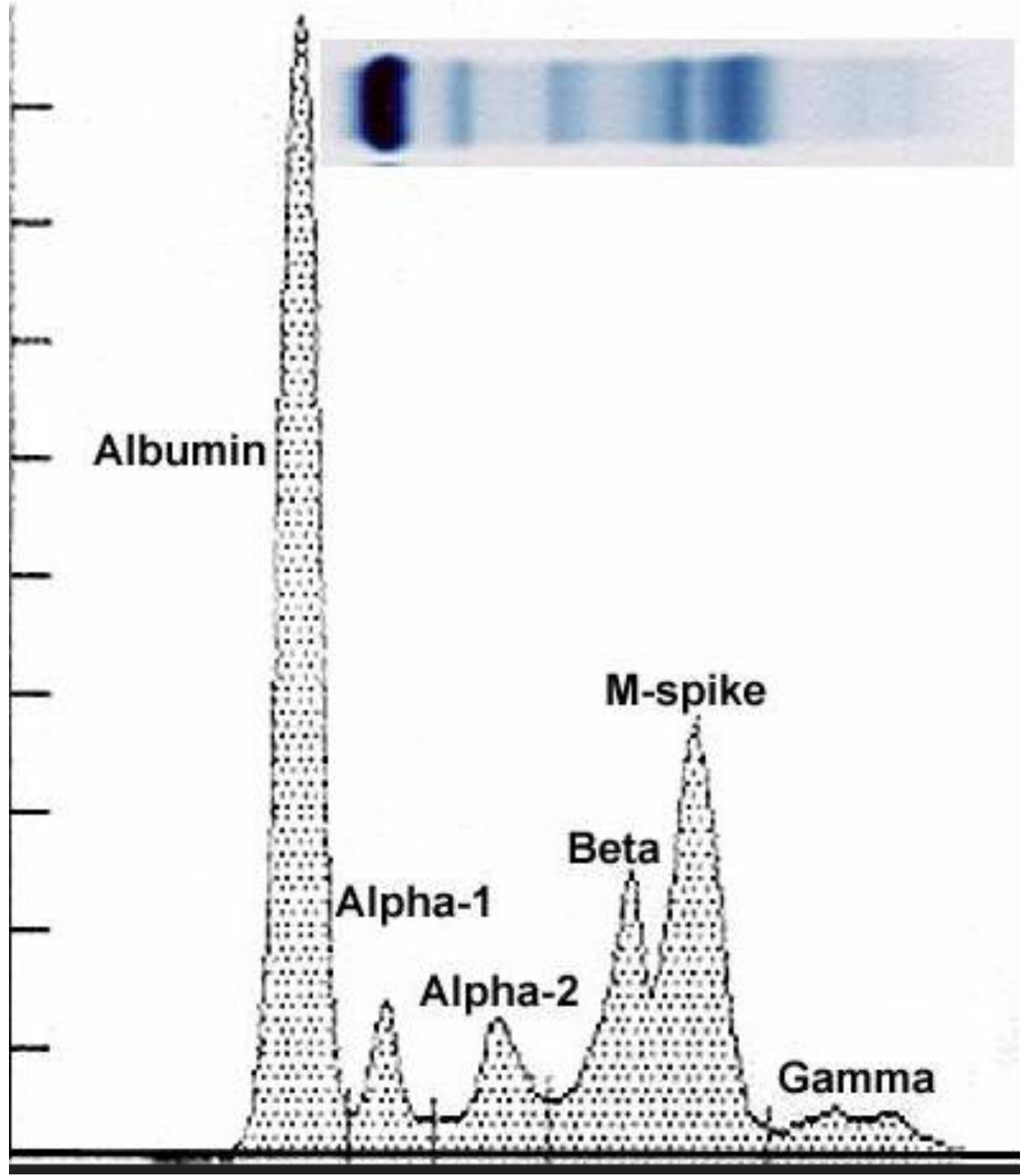
Serum Protein Electrophoresis

Advantages

- Useful screening test for monoclonal protein.
- Able to quantify the size of the M-protein
- Provides quantitative and pattern information about albumin, alpha-1, alpha-2, beta and gamma globulin

Disadvantages

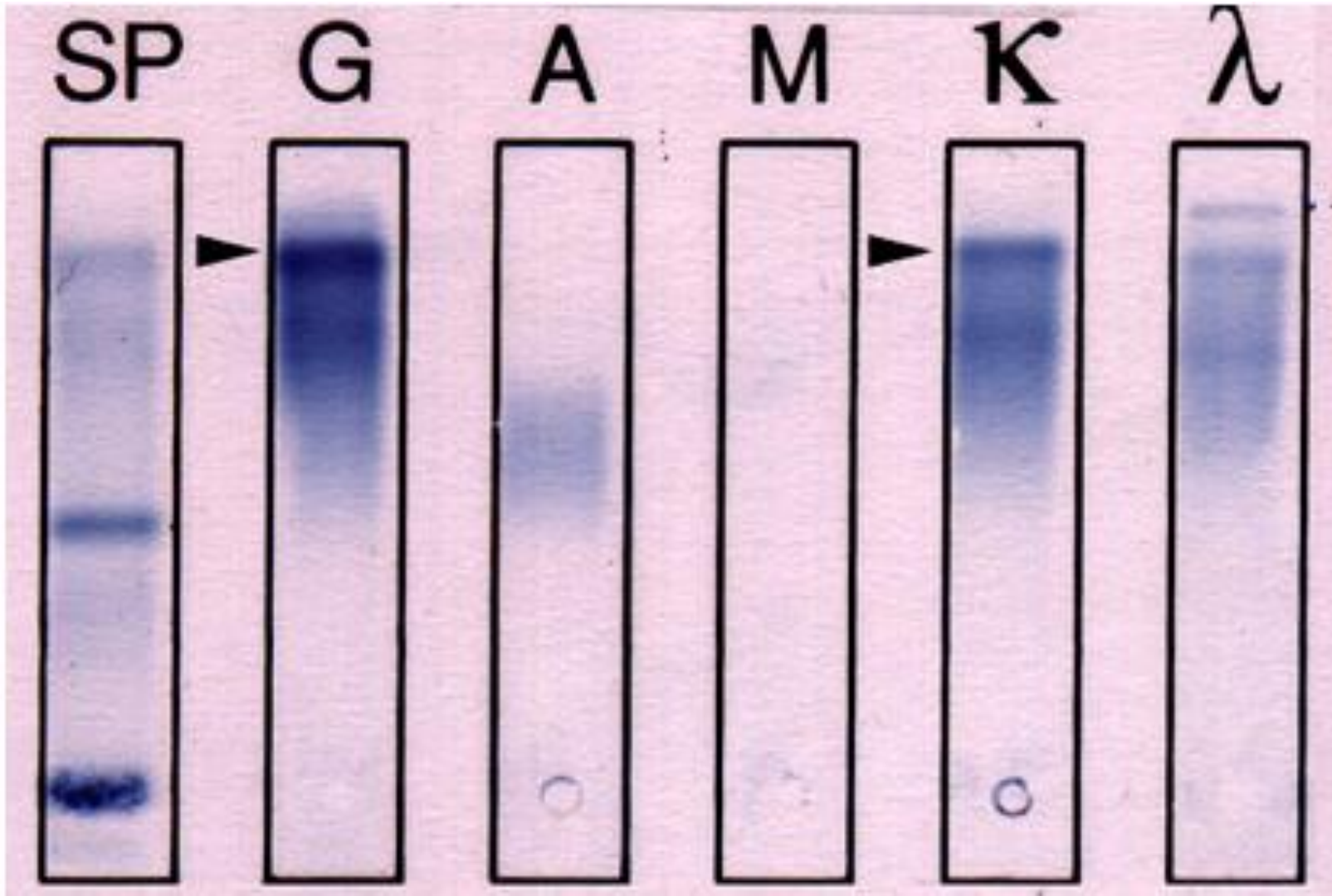
- When an M-protein is present, SPEP will not be able to provide information about the immunoglobulin heavy and light chain class.
- Not as sensitive as immunofixation at differentiating monoclonal from polyclonal gammopathy



Serum Protein Electrophoresis

Total Protein	6.7 g/dL	(6.0-8.0) g/dL
Albumin	3.80 g/dL	(3.20-5.30) g/dL
Alpha 1	0.21 g/dL	(0.10-0.40) g/dL
Alpha 2	0.82 g/dL	(0.50-1.00) g/dL
Beta	0.78 g/dL	(0.60-1.20) g/dL
Gamma	1.08 g/dL	(0.80-1.70) g/dL
	“Two M-spikes detected”	

Immunofixation: after serum electrophoresis, each sample is overlaid with a different mono-specific antibody. Precipitation occurs from formation of antigen-antibody complexes.



Immunofixation

- More sensitive than serum protein electrophoresis
- Not quantitative unless done in conjunction with electrophoresis.

Immunofixation

Gamma M Spike 1	0.18/g/dL	IgM Lambda
Gamma M Spike 2	0.62 g/dL	IgG Lambda
Note units are g/dL		

Quantitative Immunoglobulins

- Most useful test for detecting hypogammaglobulinemia
- The degree of turbidity produced by antigen-antibody reaction is measured by nephelometry
- ***Does not allow an assessment of clonality

Quantitative Immunoglobulins

IgG	942 mg/dL	700-1600 mg/dL
IgA	32 mg/dL	70-400 mg/dL
IgM	259 mg/dL	40-230 mg/dL

Quantitative immunoglobulins are measured in mg/dl...

IgG	942 mg/dL	700-1600 mg/dL
IgA	32 mg/dL	70-400 mg/dL
IgM	259 mg/dL	40-230 mg/dL
Gamma M Spike 1	0.18/g/dL	IgM Lambda
Gamma M Spike 2	0.62 g/dL	IgG Lambda

...Gamma Spikes are measured in g/dL

Calculation of meaningful IgG:

IgG	942 mg/dL	700-1600 mg/dL
IgA	32 mg/dL	70-400 mg/dL
IgM	259 mg/dL	40-230 mg/dL
Gamma M Spike 1	0.18/g/dL	IgM Lambda
Gamma M Spike 2**	0.62 g/dL	IgG Lambda

Total IgG=942 mg/dL

Monoclonal IgG=0.62 g/dL=620 mg/dL

Meaningful IgG=942-620=342 mg/dL

Calculation of meaningful IgM:

IgG	942 mg/dL	700-1600 mg/dL
IgA	32 mg/dL	70-400 mg/dL
IgM**	259 mg/dL	40-230 mg/dL
Gamma M Spike 1	0.18/g/dL	IgM Lambda**
Gamma M Spike 2	0.62 g/dL	IgG Lambda

Total IgM= 258 mg/dL

Monoclonal IgM=0.18g/dL=180 mg/dL

Meaningful IgM=259-180=79 mg/dL

Diagnosis of our patient

- Hypogammaglobulinemia in the setting of clonal gammopathy: masked by available clinical laboratory testing.

Treatment

- Our approach:
 - IVIG or subcutaneous immune globulin in patients with both low Ig and infection.
 - Our patient is receiving IVIG and is doing well so far...

Alternative Testing

- Check baseline immunoglobulin titers against specific common protein and polysaccharide antigens (tetanus, diphtheria, pneumococcus).
- Immunize
- Recheck titers in 3 weeks, anticipating a 2-4 fold increase in titers.

Diagnostic Criteria for MGUS

- M-protein <3 g/L
- Bone marrow (if done) <10% plasma cells
- Absence of end organ damage “CRAB”
 - Hypercalcemia
 - Renal insufficiency
 - Anemia
 - Bone lesions

Monoclonal Gammopathy of Undetermined Significance

- Patients exhibit no symptoms or physical findings
- M-protein usually discovered unexpectedly
- 70% IgG
- 15% IgM
- 12% IgA
- 3% Biclonal
- Up to 20% may consist only of Ig light chain

The New England Journal of Medicine

**A LONG-TERM STUDY OF PROGNOSIS IN MONOCLONAL GAMMOPATHY
OF UNDETERMINED SIGNIFICANCE**

**ROBERT A. KYLE, M.D., TERRY M. THERNEAU, PH.D., S. VINCENT RAJKUMAR, M.D., JANICE R. OFFORD, B.S.,
DIRK R. LARSON, M.S., MATTHEW F. PLEVAK, B.S., AND L. JOSEPH MELTON III, M.D.**

NEJM Vol 346, No 8. Feb 21, 2002 P 564-568

The concentrations of normal polyclonal or background immunoglobulins are reduced in 93 percent of patients with multiple myeloma²¹ but are thought to be normal in those with benign monoclonal gammopathy. However, we found reduced concentrations of uninvolved immunoglobulins in 29 percent of our original cohort of 241 patients with MGUS⁶ and in 38 percent of the 840 patients in the current group in whom immunoglobulins were measured. Such a

The risk of bacteremia in patients with MGUS

- Danish study:
 - 40 episodes of bacteremia versus 18 episodes expected
 - ~5000 patient-years of follow-up
 - Mean follow-up 3.8 years/patient
- Swedish study:
 - Two-fold increased risk of bacterial and viral infections in MGUS
- Eur J Haematol. 1998;Aug 61 (2);140-4
Gregersen H et al
- Haematologica: 2012;97(6), p854
- Kristinsson S et al

Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis.

Raanani P, Gafer-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O.

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Results:

- 1. Infection rate cut in half**
- 2. Survival rate not altered**

Summary

1. We described a gentleman with masked hypogammaglobulinemia in the setting of clonal gammopathy.
2. We describe the interpretation of SPEP, immunofixation, and quantitative immunoglobulins
3. The infection rate is doubled in patients with MGUS.
4. The role of IVIG in MGUS hasn't been well-studied, but in CLL and Myeloma, the rate of infection is reduced by 50% with IVIG but without improvement in overall survival.