Management of Confusing Results

2024 ACP Washington Chapter Meeting

Outpatient Pre-Course

Sheida Aalami, MD

I have no financial or other conflicts of interest.

I am motivated by things that confuse me.

Objectives

1) Utilize a structured approach to the evaluation of macrocytosis

2) Understand what an SPEP is and the appreciate what differentiates low risk MGUS

3) Interpret positive rheumatoid factor results in an appropriate clinical context

Case 1

DS is a 78-year-old who presents for his annual visit. He has a history of well-controlled hypertension and hyperlipidemia but is otherwise healthy. His medications are amlodipine 10mg daily and atorvastatin 20mg daily. He has no concerns today but wants to get his annual bloodwork done.

Against your better judgement, you order a screening CBC which shows the following:

Case 1 continued

WBC 7.57 K/uL

RBC 4.4 Mil/uL

Hgb 14.4 g/dL

Hematocrit 43.3 %

MCV 105 fL

RDW 13.7%

Platelets 157 K/uL

Case 1 continued

WBC 7.57 K/uL

RBC 4.4 Mil/uL

Hgb 14.4 g/dL

Hematocrit 43.3 %

MCV 105 fL

RDW 13.7%

Platelets 157 K/uL

Case 1 continued

What is going on?

What do you do next?

Macrocytosis

- Morphologic term; not a specific disease
- Higher than normal MCV (mean corpuscular/cell volume), measured in femto-liters (10^{-15} liter)
- Can also be diagnosed by peripheral smear (large RBC's)

Three Big Questions

- Is it real?

Three Big Questions

Is it real?

RBC’s clumped, hyperglycemia, cold agglutinins

Three Big Questions

Does this patient need a hematologist?

Refer IF neutropenia or thrombocytopenia

Three Big Questions

Why is this happening?

Macrocytosis

Top 3 causes:

1) Alcohol
2) Hemolysis
3) B12/folate deficiency

Macrocytosis: Alcohol

- Often underreported: 11-37% (Shafaat et al, 2024)
- Macrocytosis develops before anemia
- 80 g/day sufficient to cause macrocytosis

Macrocytosis: Hemolysis

- Clues: robust reticulocytosis, spherocytes on smear

Macrocytosis: B12/folate deficiency

- Severe macrocytosis ie MCV>110
- Vegan diet
- Symptoms (neuropathy)

Macrocytosis

Top 3 causes:

1) Alcohol
2) Hemolysis
3) B12/folate deficiency

Other causes

4) Medications
5) Thyroid disease
6) Other vitamin deficiencies: Cu
7) HIV

Drug Induced Macrocytosis

allopurinol	nitrofurantoin
ampicillin	nitrous oxide
cholestyramine	omeprazole
erythromycin	phenytoin
estrogens	primidone
famotidine	triamterene
metformin	trimethoprim
methotrexate	valproic acid

Macrocytosis: My Approach

1) Ask everyone about alcohol
2) Get some more labs: CBC with diff and peripheral smear, CMP, reticulocytes, haptoglobin/LDH?, B12, folate, TSH, HIV, Cu?
3) Review medication list
4) Monitor q6-12 months, monitor for cytopenias

    → Could this be MDS?

Case 2

MM is a 70-year-old man who presents for follow-up. Your colleague saw him in clinic last month for evaluation of anemia, and he received a letter in the mail after his visit noting “abnormal SPEP results.”

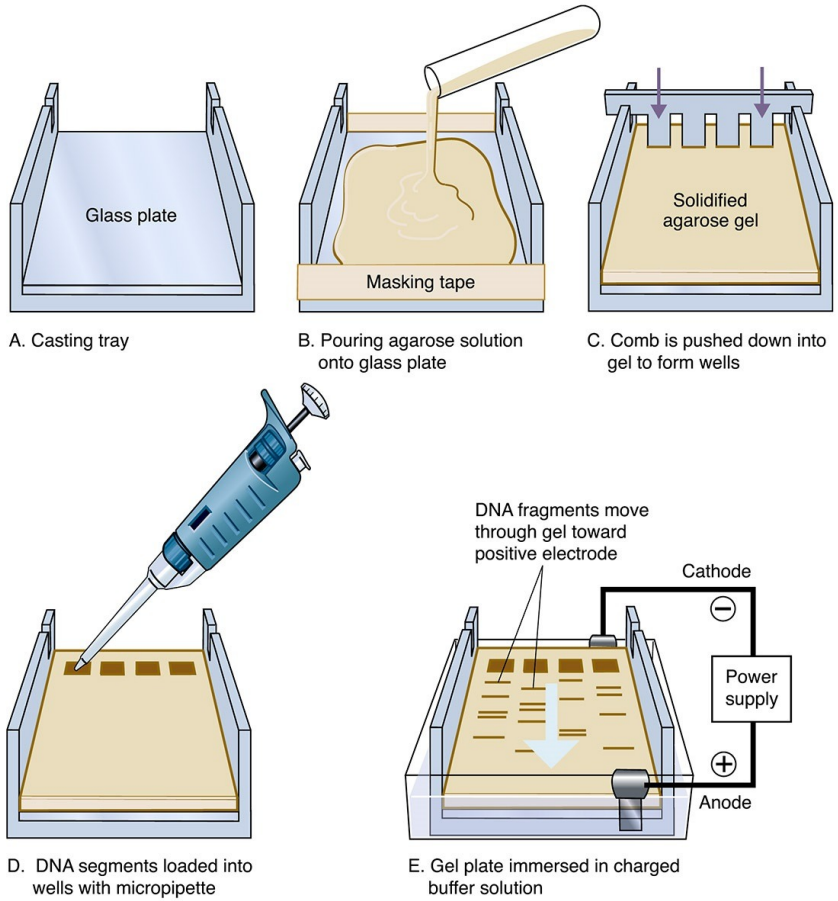
He does not know what this means but he has done some reading online and is worried he has blood cancer. He looks to you, his primary care doctor, to explain.

Abnormal SPEP

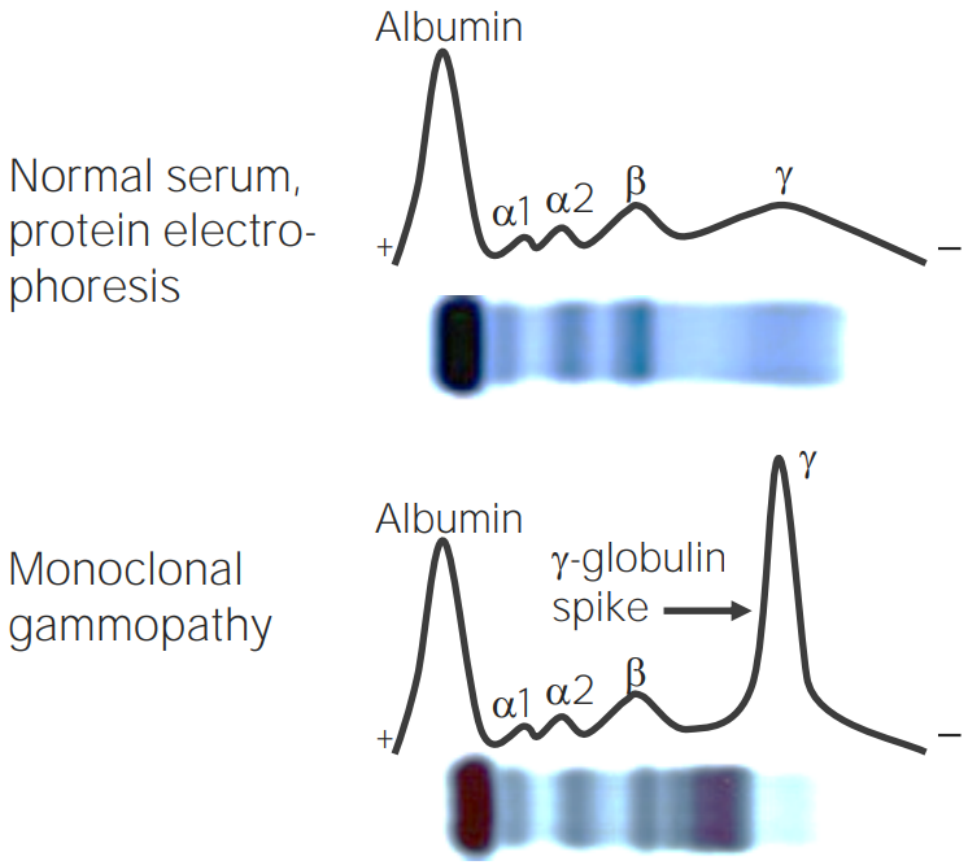
SPEP

- Serum Protein Electrophoresis AKA SPEP
- What proteins?
  - I know about albumin
  - What is globulin?

Electrophoresis



What is an SPEP

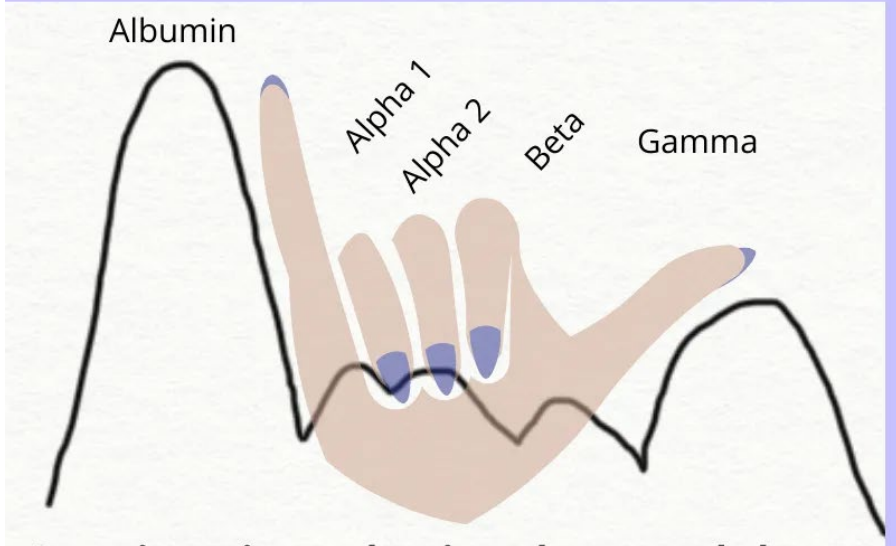


It's an SPEP, brah

THE CURB SIDERS INTERNAL MEDICINE

SPEP = Serum Protein Electrophoresis

AKA The Electric Protein Race



Proteins migrate by size, shape, and charge

In Myeloma:

↓ Albumin

Alpha 1

Alpha 2

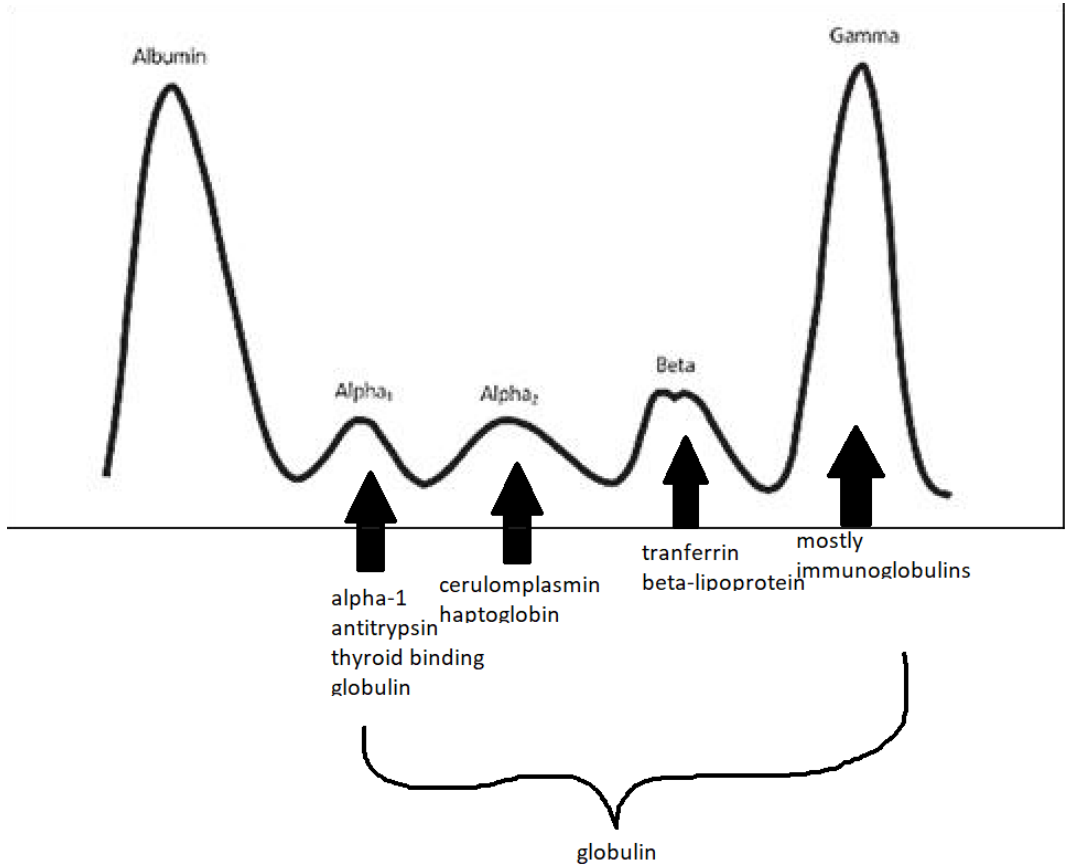
Beta

↑ Gamma

(usually)

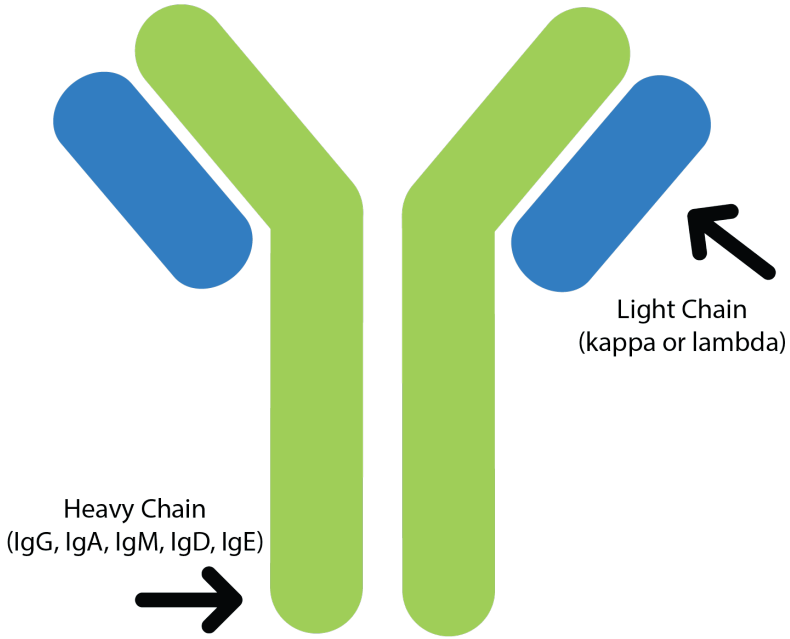
The right-handed Shaka Sign (def: To "hang loose", Hawaiian origins) is a good way of remembering how the SPEP protein peaks normally look--with Albumin being the largest.

What's In an SPEP



Thebloodproject.org, with additions by me

Immunoglobulins= Antibodies



SPEP versus Immunofixation

- SPEP answers: is there an M-spike? How much?
- Immunofixation answers: What is the M-spike made of?

What About Free Light Chains?

- Why send free light chains?
  - M-spike can be free light chain only
  - The ratio is important

Our Patients Results

- IgG kappa M protein 0.7 g/dL
- Kappa free light chains 1.87mg/dL (0.33-1.94)
- Lambda free light chains 1.52 mg/dL (0.57-2.63)
- Free light chain ratio 1.23 (0.26-1.65)

MGUS

- Monoclonal Gammopathy of Undetermined Significance

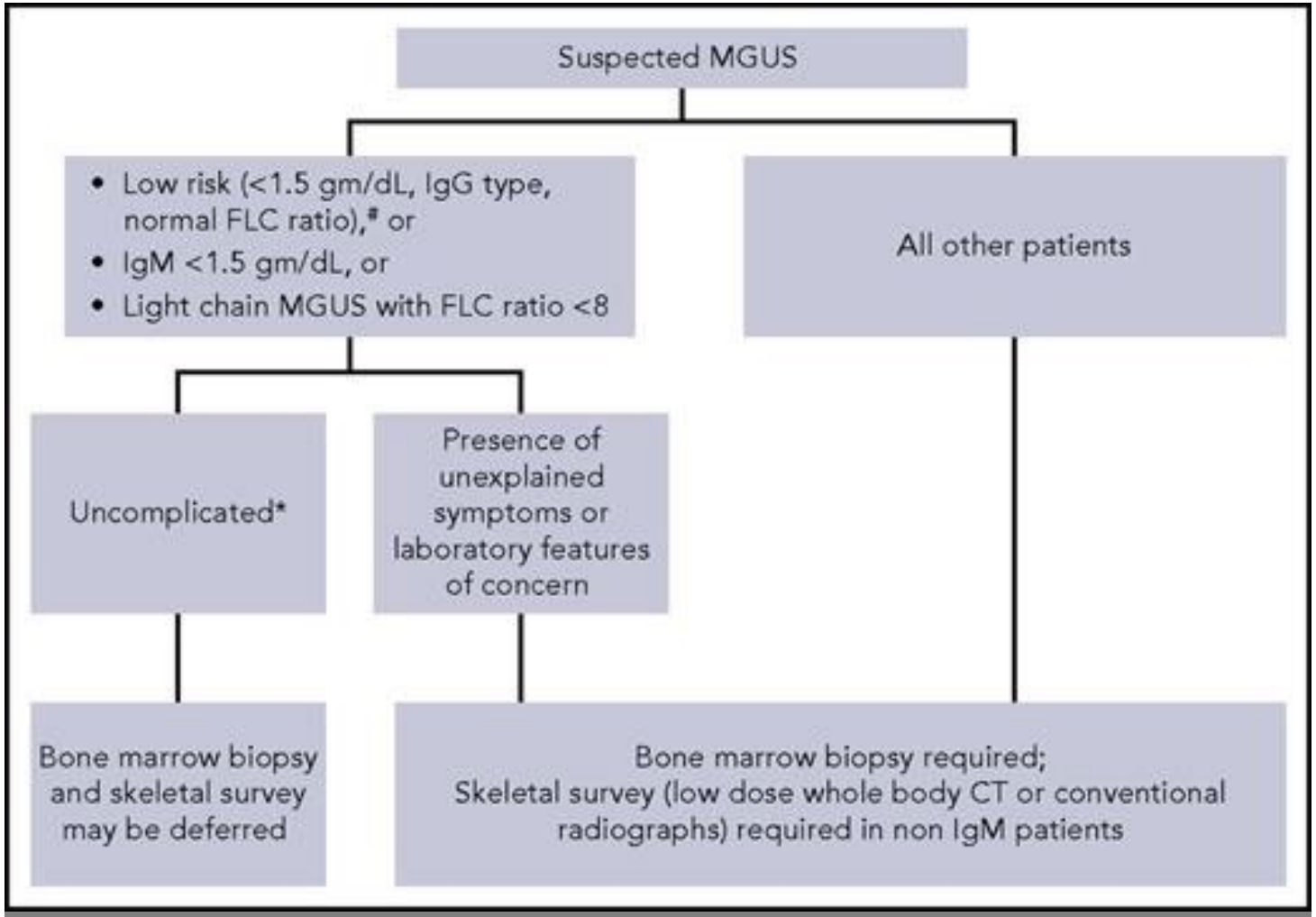
- Requires:
  1) M-spike <3g/dL
  2) Clonal bone marrow plasma cells <10%
  3) No end organ damage
     - Hypercalcemia >11.5 mg/dL
     - Renal dysfunction Cr >2 mg/dL
     - Anemia Hgb<10 g/dL or 2g/dL below normal
     - Bone lesions

MGUS

- Monoclonal Gammopathy of Undetermined Significance

- Requires:
  1) M-spike <3g/dL
  2) Clonal bone marrow plasma cells <10%
  3) No end organ damage
     - Hypercalcemia >11.5 mg/dL
     - Renal dysfunction Cr >2 mg/dL
     - Anemia Hgb<10 g/dL or 2g/dL below normal
     - Bone lesions

Do All Patients Need a Bone Marrow Biopsy and Imaging?



Go & Rajkumar, 2018

Low Risk IgG MGUS

- Probability bone marrow plasma cells>=10%: 4.7% (Mangiacavalli et al, 2013)
- Probably bone lesion: 1.5% (Mangiacavalli et al, 2013)
- Lifetime risk of progression 2% (Rajkumar et al, 2005)

Free Light Chains in Kidney Disease

- Serum Free Light Chains cleared by kidneys
- Both Kappa and Lamba light chain levels rise, but Kappa levels tend to rise higher
- Revised renal reference range: FLC ratio of 0.37-3.1 (Hutchinson et al, 2008)

Reminder: MGUS increases with age

Age	% of Population with MGUS
50’s	1-3%
70’s	5%
85+	7.5%

Kyle et al, 2006

Abnormal SPEP: My Approach

1) Check SPEP with immunofixation (reflexive at my institution), free light chains, CBC and CMP
2) Refer to or E-consult hematology often, except maybe in low-risk MGUS:
   - IgG or IgM <1.5g/dL
   - normal free light chain ratio
   - no symptoms

Case 3

JK is a 65-year-old with chronic hepatitis B who presents for an acute visit for hand pain. The pain is primarily located at the base of his left thumb, though he notices some pain in his right thumb, too. He has no joint pain elsewhere. He notices it is worse at the end of the day after playing guitar. He otherwise feels quite well.

On exam, his HR is 78 and BP 134/72. There is some mild tenderness to palpation at the left CMC joint, otherwise there is no tenderness to palpation in the bilateral hand joints. No redness or synovitis.

Case 3 continued

He tells you he was seen for a similar issue at urgent care where he had labs done (you can't view the results) and was told to follow-up with his primary care doctor because his blood tests showed he has rheumatoid arthritis.

Sensitivity and Specificity Depend on Population

- In a metanalysis, rheumatoid factor 69% sensitive and 85% specific (Nishimura et al, 2007)
- 96% specific in young healthy population (<40) (Nishimura et al, 2007)
- When low risk, positive test is more likely false positive

Rheumatoid Factor Is Positive in Other Disease States

Condition	Frequency of Rheumatoid Factor %
Age>60	5-25
Bacterial endocarditis	25-50
Hepatitis B or C	20-75
Sarcoidosis	3-33
Asbestosis	30
Interstitial Pulmonary Fibrosis	10-50
Primary Biliary Cirrhosis	45-70
Malignancy	5-25
After multiple immunizations	10-15
Other viral infection	10-65

Schmerling & Delbanco, 1991

Positive RF: My Approach

1) Interpret RF in clinical context
2) Be wary of positive RF in otherwise asymptomatic older adults
3) Screen for other disease

References

1. Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. *Blood* (2018) 131 (2): 163–173.

2. Hoffbrand V, Provan D. ABC of clinical haematology. Macrocytic anaemias. BMJ. 1997 Feb 8;314(7078):430-3

3. Hutchison CA, et al. Quantitative assessment of serum and urinary polyclonal free light chains in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2008 Nov;3(6):1684-90.

4. Koury MJ, Hausrath DJ. Macrocytic anemias. Curr Opin Hematol. 2024 May 1;31(3):82-88.

5. Kyle RA et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006 Mar 30;354(13):1362-9.

6. Mangiacavalli S et al. Monoclonal gammopathy of undetermined significance: a new proposal of workup. Eur J Haematol. 2013 Oct;91(4):356-60.

7. Nishimura K et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007;146(11):797.

8. Rajkumar SV et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005 Aug 1;106(3):812-7

9. Shafaat SS et al. A Cross-Sectional Study for the Spectrum of Clinical Diagnosis in Patients Presenting With Macrocytosis. Cureus. 2024 Feb 22;16(2):e54702.

10. Shmerling RH, Delbanco TL. The rheumatoid factor: An analysis of clinical utility, Am J Med 1991; 91:528

Questions?