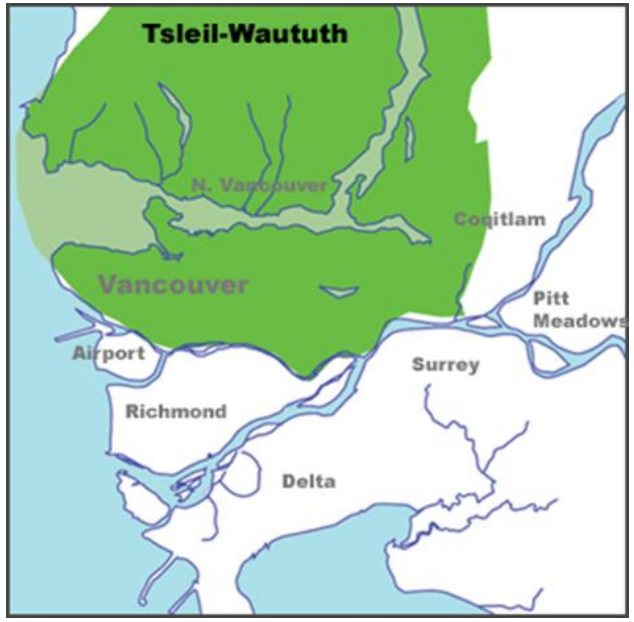
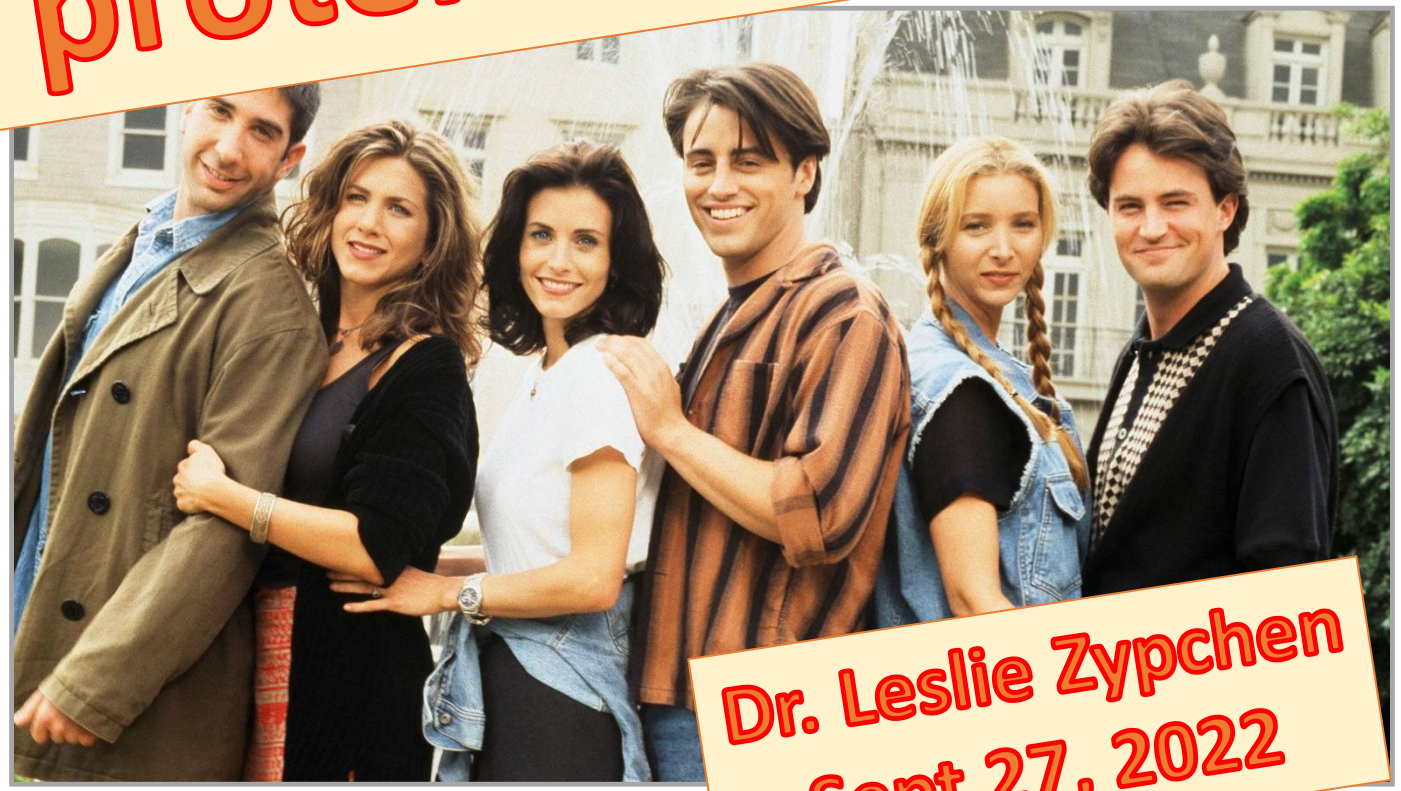
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



M proteins and friends



Dr. Leslie Zypchen

Sept 27, 2022

Conflict of interest

- Research support: GlaxoSmithKline, Pfizer

- Mitigating potential bias: Will not be discussing drugs from these clinical trials

Objectives

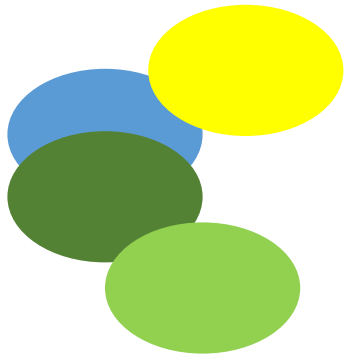
1. Monoclonal protein **basics and testing**

2. **Common** monoclonal protein disorders
   - Monoclonal gammopathy of undetermined significance
   - Myeloma

3. **Less common** stuff
   - Monoclonal gammopathy of **clinical** significance
   - Polyclonal hypergammaglobulinemia

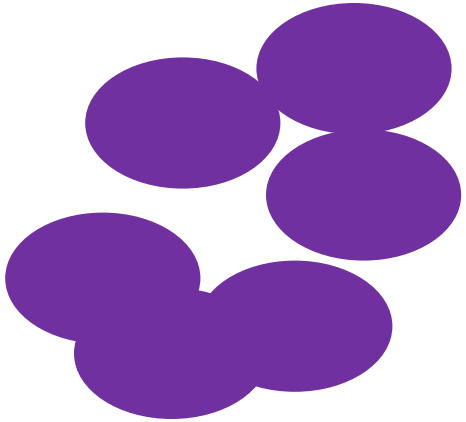
Monoclonal proteins basics and testing

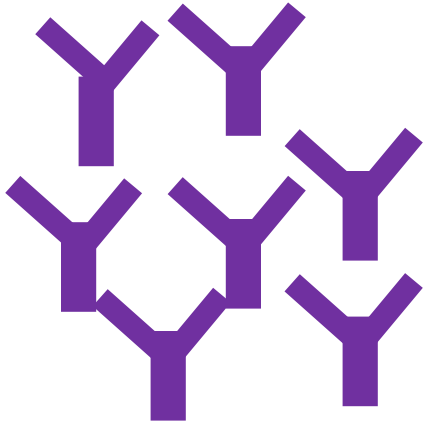
Plasma cell review



Normal polyclonal plasma cells | Normal polyclonal antibodies | Normal and good job

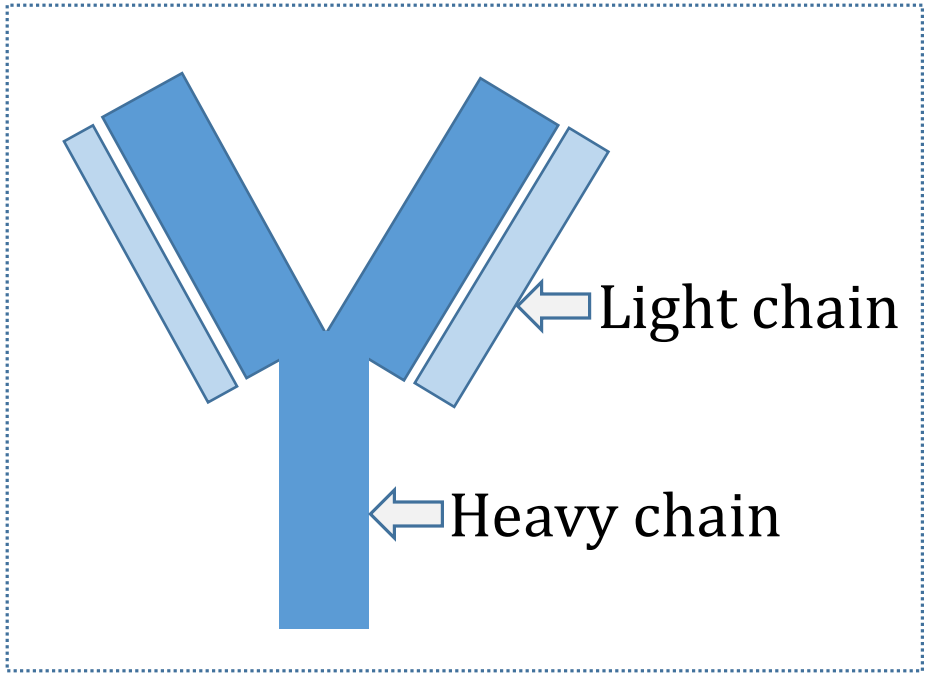
---





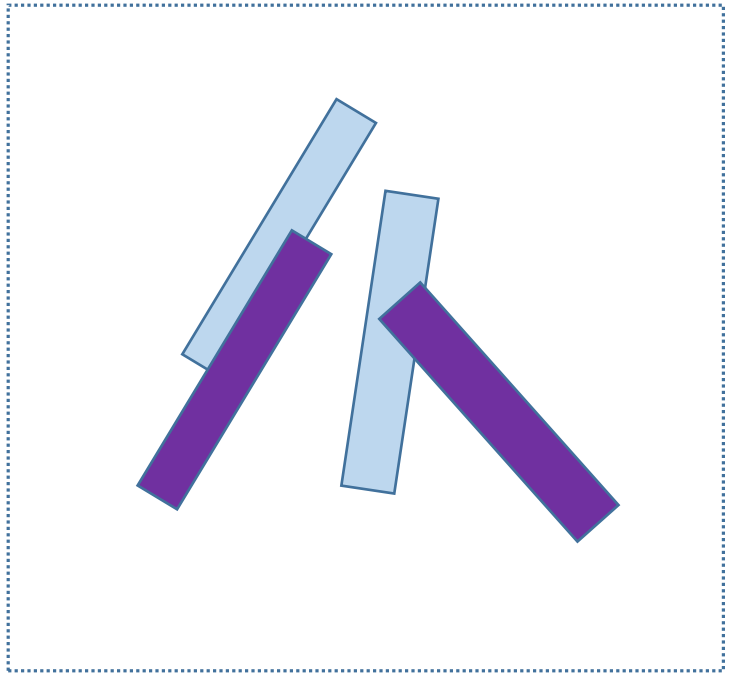
Abnormal **clonal** plasma cells | Abnormal **monoclonal** PROTEIN! just mischief

Antibody (protein) review



IgG
IgA
IgM
IgD
IgE

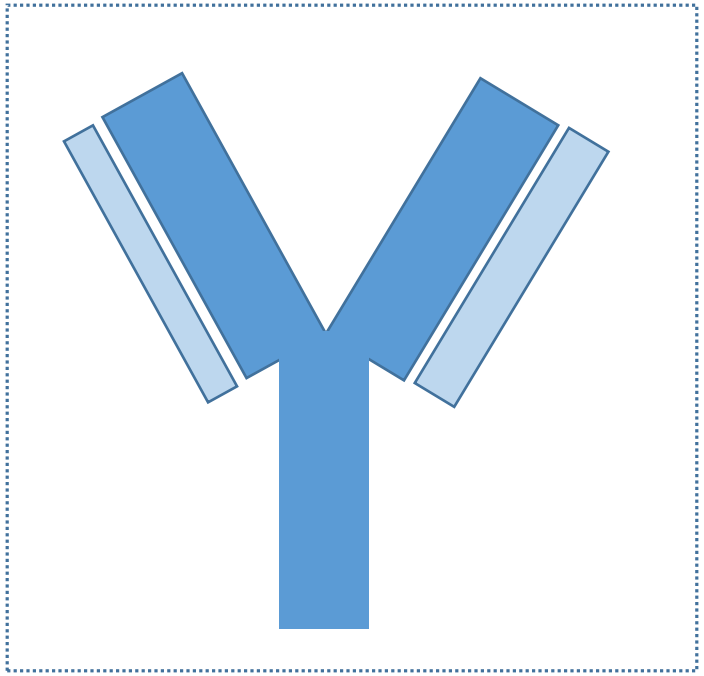
"Intact" monoclonal protein



Kappa
Lambda

"Free" light chains

When it comes to myeloma

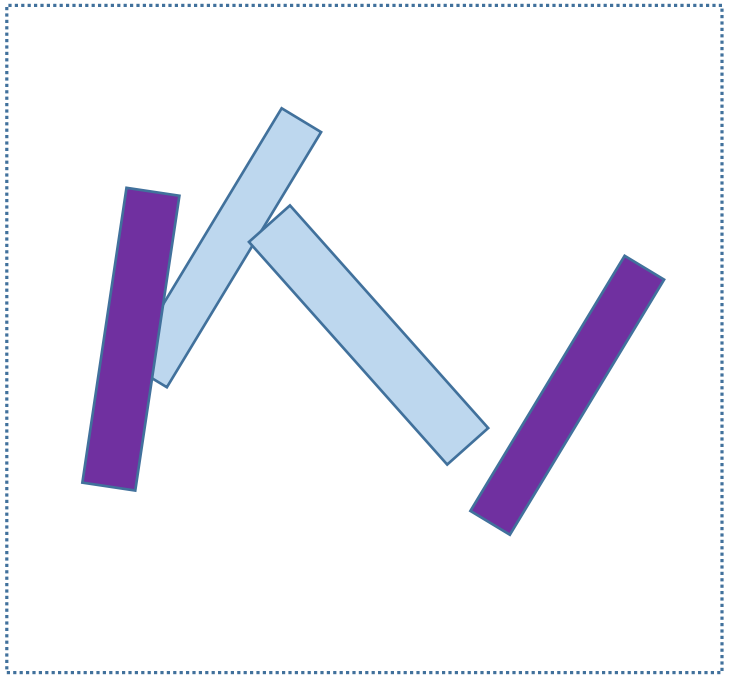


IgG

IgA

Light chain only

IgD, biclonal, IgM, nonsecretory



IgM M protein ≠ myeloma. Instead think **lymphoma!**

Take home message

IgM M protein ⇏ myeloma. Instead think **lymphoma!**

Big IgM M protein

- Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia)

Small IgM M protein

- Other low grade lymphomas (CLL, marginal zone lymphoma)
- Less advanced lymphoplasmacytic lymphoma
- MGUS

Protein testing

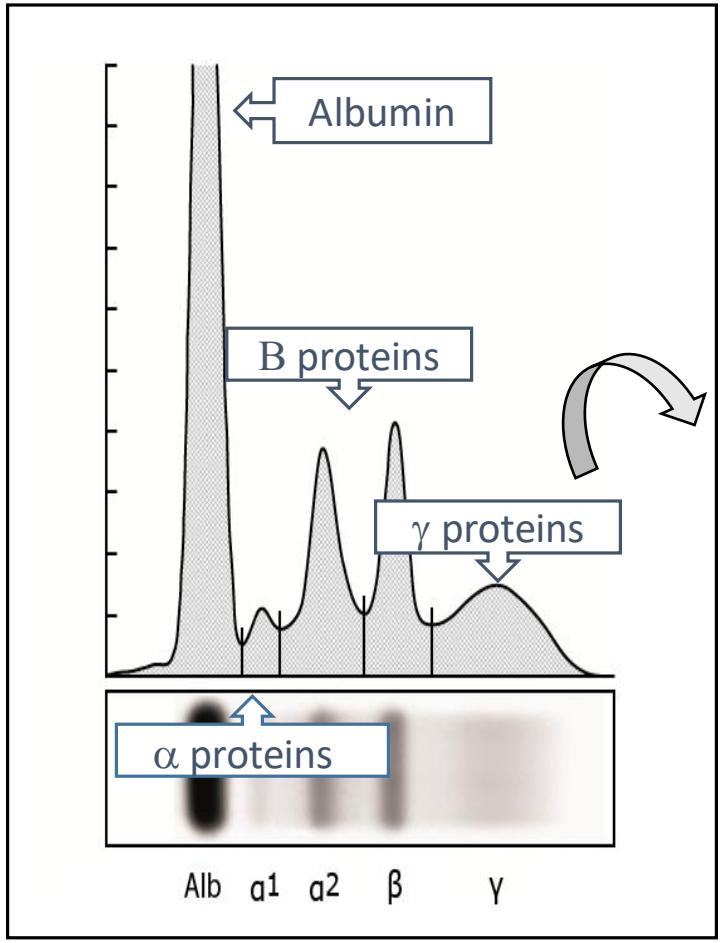
What test?

1. Serum/urine protein electrophoresis and immunofixation
2. Quantitative immunoglobulins
3. Free light chain assay

What information?

1. **Amount** of protein
2. **Isotype** of protein
3. **Monoclonal vs. polyclonal**

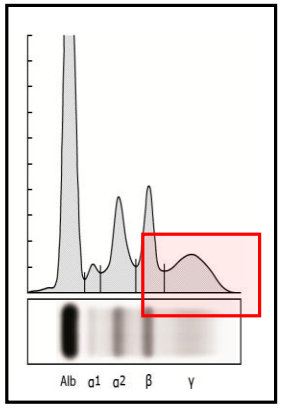
Normal SPEP

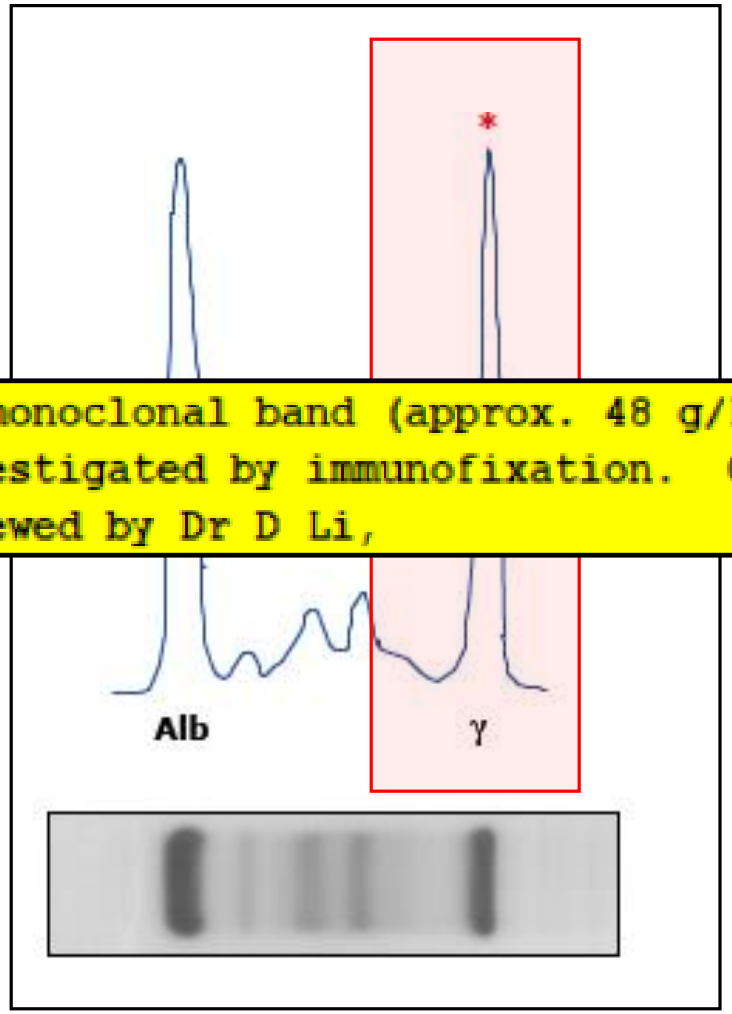


Immunoglobulins!

Abnormal SPEP

- ✓ Amount of protein
- Isotype of protein
- ✓ Polyclonal vs. monoclonal

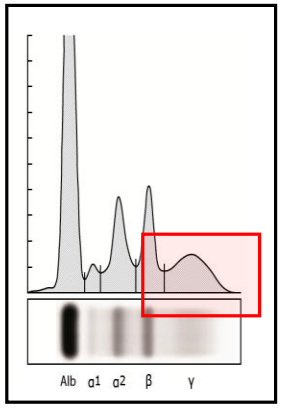


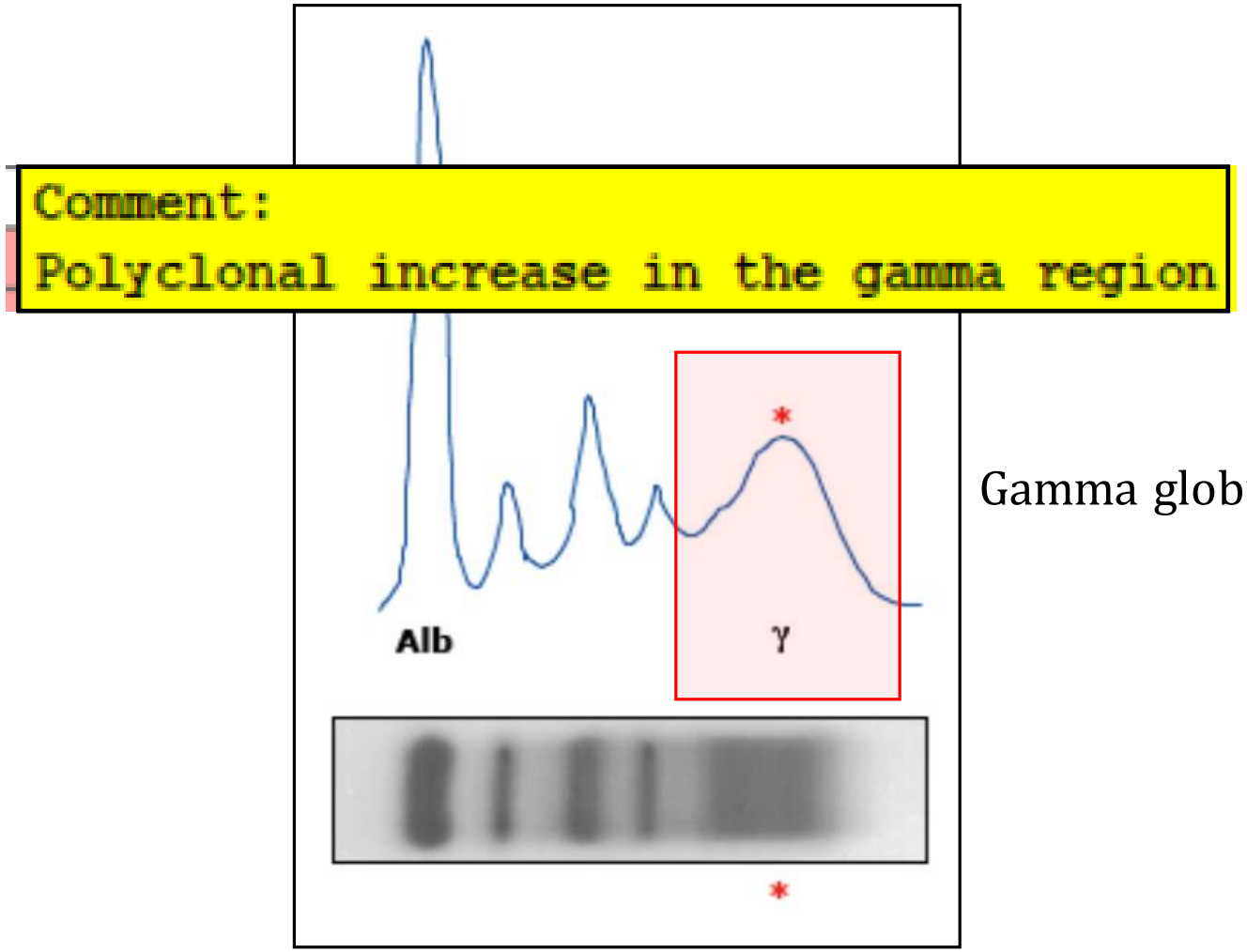


There is a dense monoclonal band (approx. 48 g/L) in the beta 2 region. This will be investigated by immunofixation. Gamma globulins are decreased. Reviewed by Dr D Li,

Another abnormal SPEP

- ✓ Amount of protein
- Isotype of protein
- ✓ Polyclonal vs. monoclonal

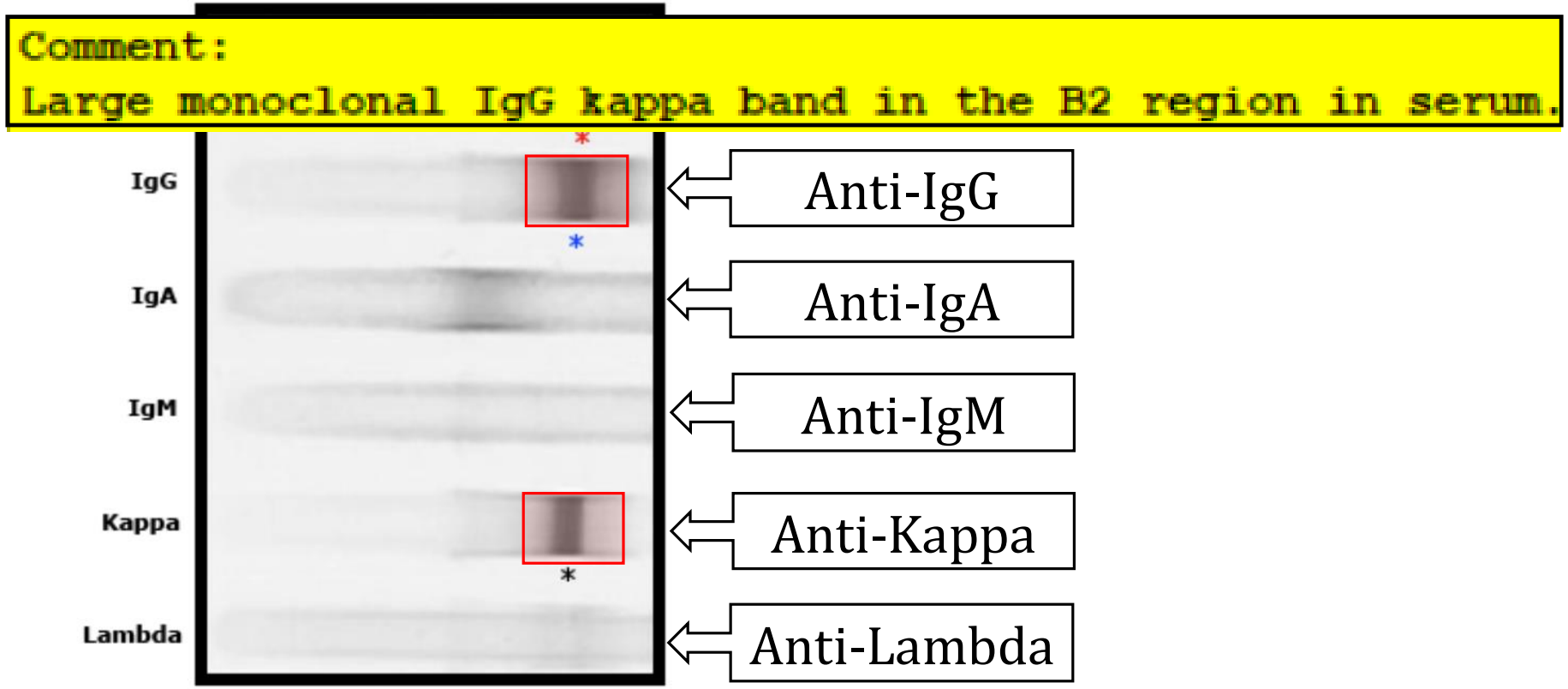




Gamma globulin = 30 g/L (N <15 g/L)

And immunofixation!

- ✓ Amount of protein
- ✓ Isotype of protein
- ✓ Polyclonal vs. monoclonal



Take home message

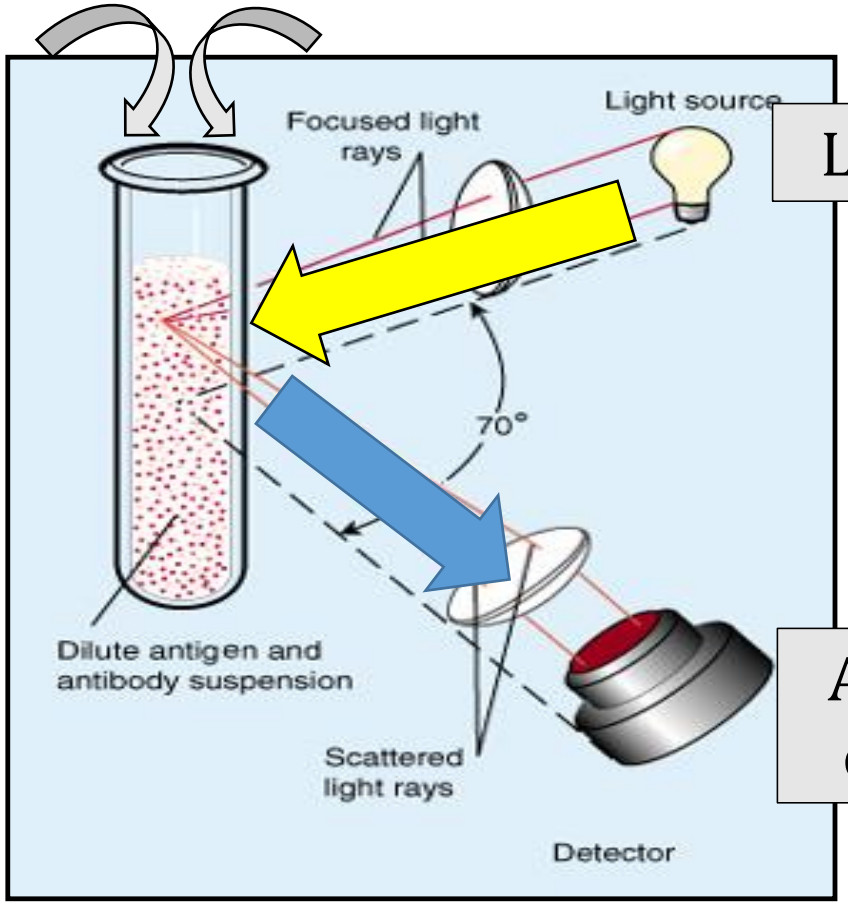
When interpreting SPEP and immunofixation, **all the info is in the comment!**

Quantitative immunoglobulins

Patient serum

Anti-IgG (or anti-IgA or IgM)

Nephelometry



Light source

Amount of scatter detected & compared to standard curve

Abnormal quantitative immunoglobulins

- ✓ Amount of protein
- ✓ Isotype of protein (heavy chain)
- Polyclonal vs. monoclonal

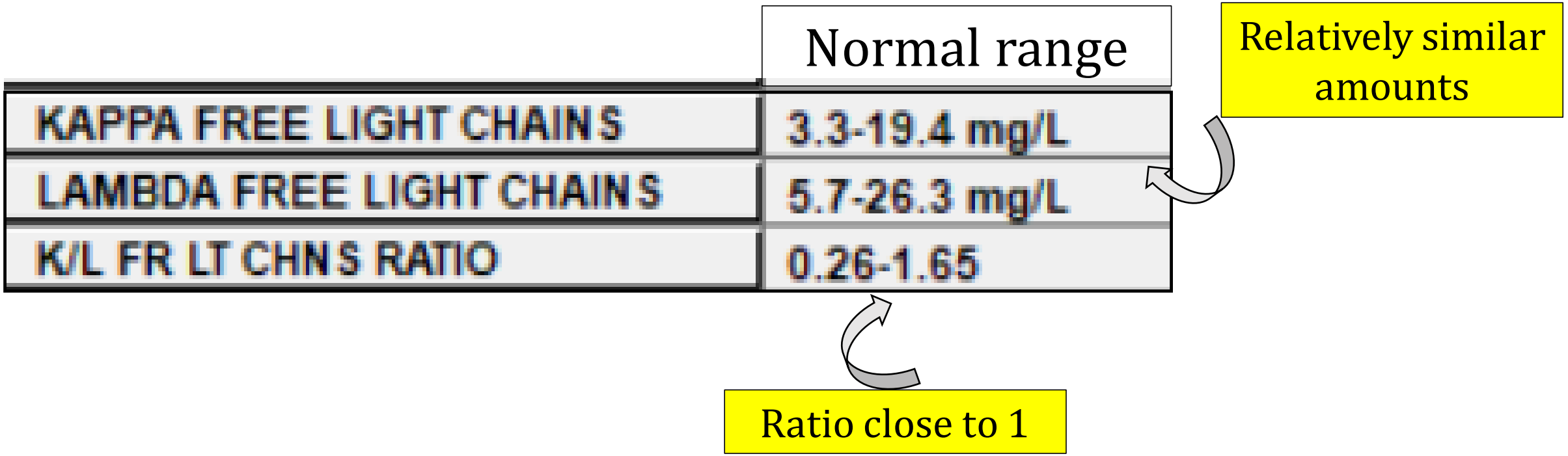
Very increased IgG

IMMUNOGLOBULIN A	0.70-4.00 g/L	4.36 h
IMMUNOGLOBULIN G	6.7-15.2 g/L	39.2 h
IMMUNOGLOBULIN M		1.33

Severe hypogammaglobulinemia

IMMUNOGLOBULIN A	0.70-4.00 g/L	<0.08 I @a1
IMMUNOGLOBULIN G	6.7-15.2 g/L	2.7 I
IMMUNOGLOBULIN M	0.40-2.30 g/L	<0.05 I

Free light chain assay (also nephelometry)



Abnormal free light chain assays

- ✓ Amount of protein
- ✓ Isotype of protein (light chain)
- ✓ Polyclonal vs. monoclonal

Monoclonal kappa free light chain

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	595.0 h
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	2.4 l
K/L FR LT CHNS RATIO	0.26-1.65	247.92 h

Monoclonal lambda free light chain

KAPPA FREE LIGH		1.4 l
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	16608.4 h
K/L FR LT CHNS RATIO	0.26-1.65	See Detail @a7

Abnormal free light chain assays?

Mild polyclonal hypergammaglobulinemia

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	25.6 h
LAMBDA FREE LIGHT CHAINS	[illegible]	[illegible] h
K/L FR LT CHNS RATIO		

Hypogammaglobulinemia

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	3.2 l
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	2.1 l
K/L FR LT CHNS RATIO		52

Mild kappa excess

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	40.4 h
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	25.7
K/L FR LT CHNS RATIO	0.26-1.65	1.57

Take home message

When interpreting FLC assays, mostly look at the **ratio**

Minor abnormalities in FLC assays often **don't matter**

Protein testing

What test?

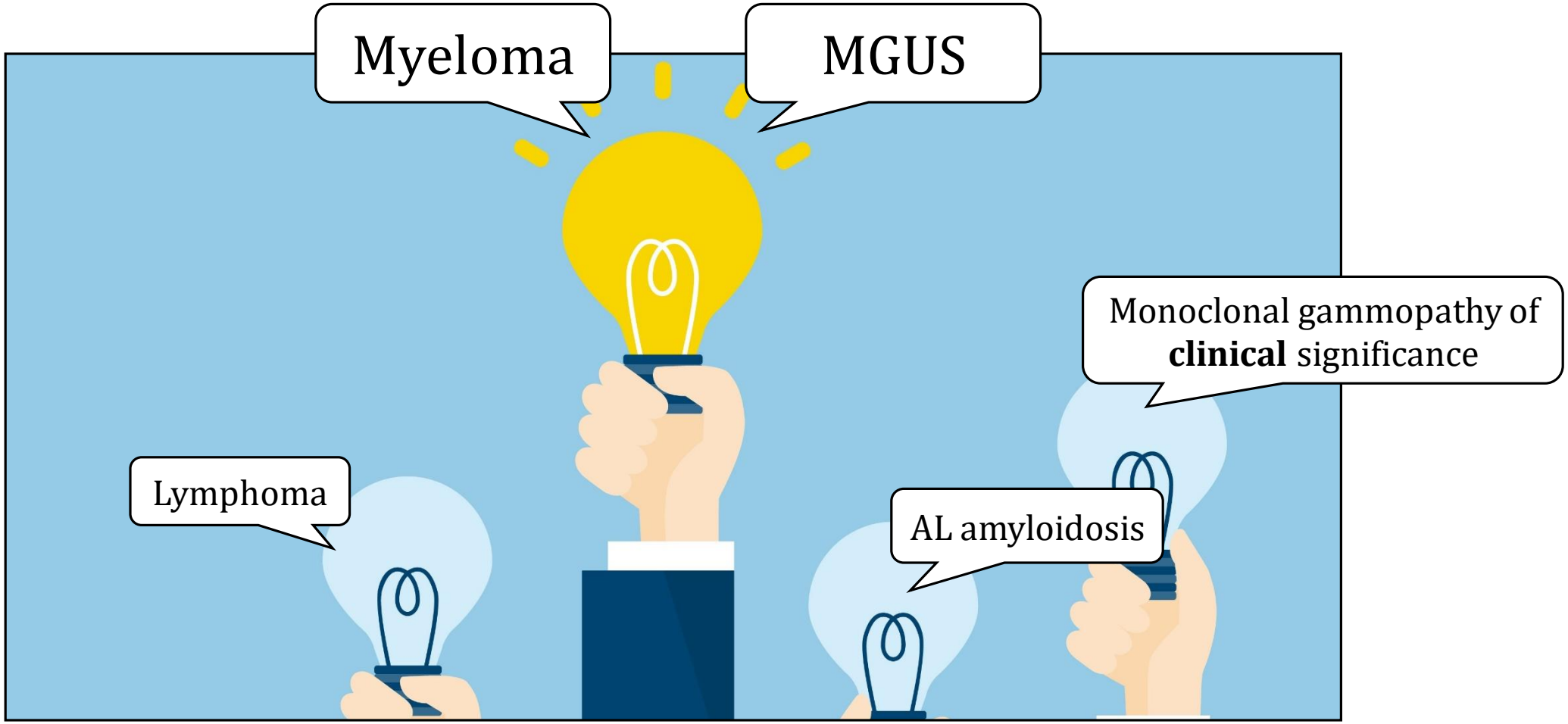
1. Serum/urine protein electrophoresis and immunofixation
   - ✓ Amount of protein
   - ✓ Isotype of protein **(immunofixation)**
   - ✓ Monoclonal vs. polyclonal
2. Quantitative immunoglobulins
   - ✓ Amount of protein
   - ✓ Isotype of protein (**heavy chain)**
   - ✗ Monoclonal vs. polyclonal
3. Free light chain assay
   - ✓ Amount of protein
   - ✓ Isotype of protein **(light chain)**
   - ✓ Monoclonal vs. polyclonal

INTERLUDE

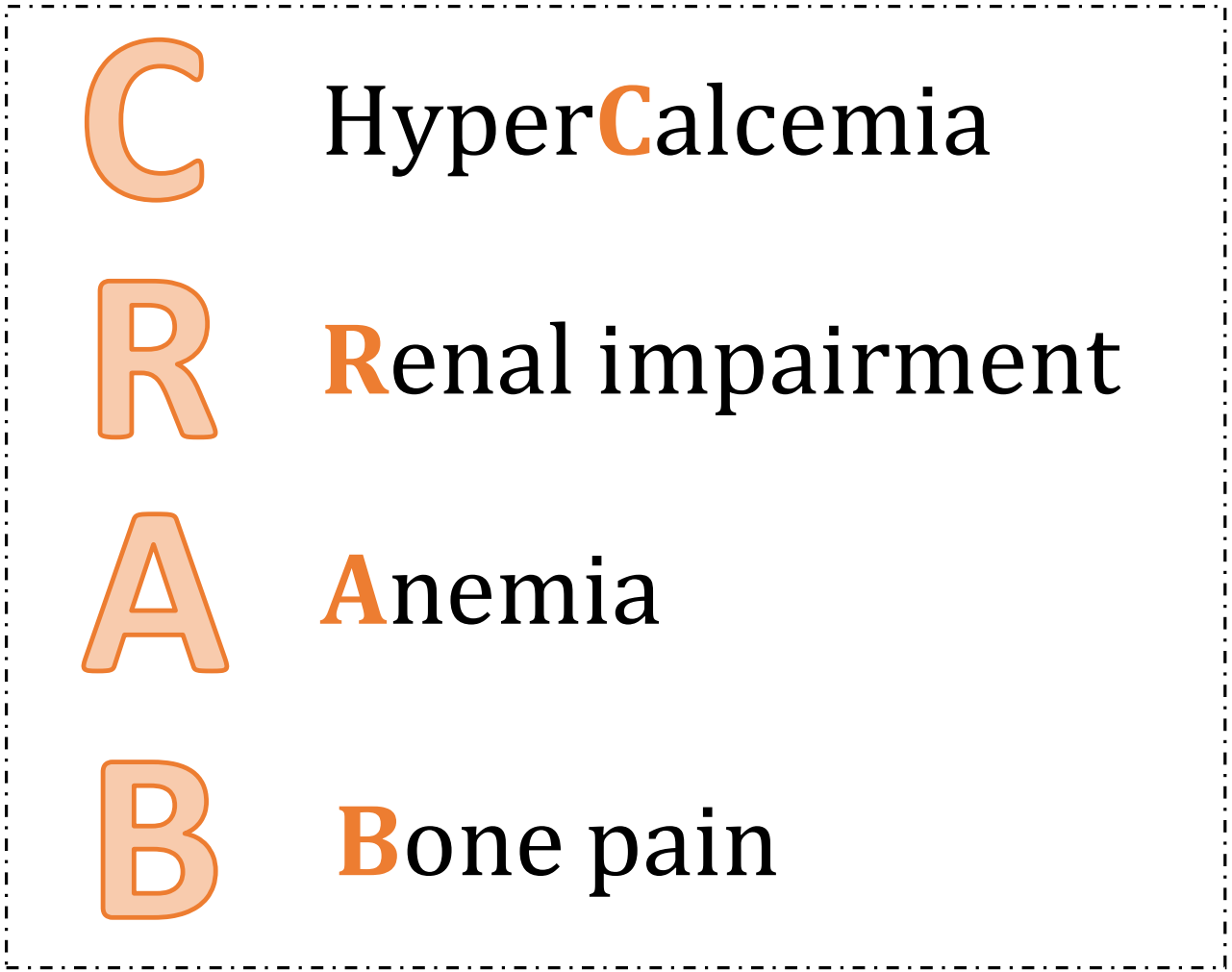
COFFEE & TEA

Common monoclonal protein disorders

So my patient has an M protein



Myeloma, it's all about the CRAB



What is MGUS?

An **asymptomatic premalignant clonal** plasma cell or lymphoplasmacytic **proliferative** disorder

Common! And increases with age

Overall	4.2%
50-59 yr	1.7%
>80 y	6.6%

By definition:

- Asymptomatic (=NO CRAB criteria!)
- M-protein <30 g/L

What is myeloma?

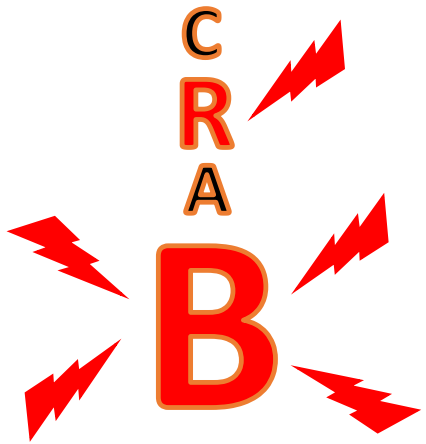
A **very morbid** hematologic **malignancy** characterized by proliferation of **clonal plasma cells** which produce a **monoclonal immunoglobulin**

Not common! (7/100,000 per yr). But relatively common amongst hematologic malignancies (20%)

By definition:

- At least one CRAB manifestation

And I mean morbid



Summary, MGUS vs. myeloma

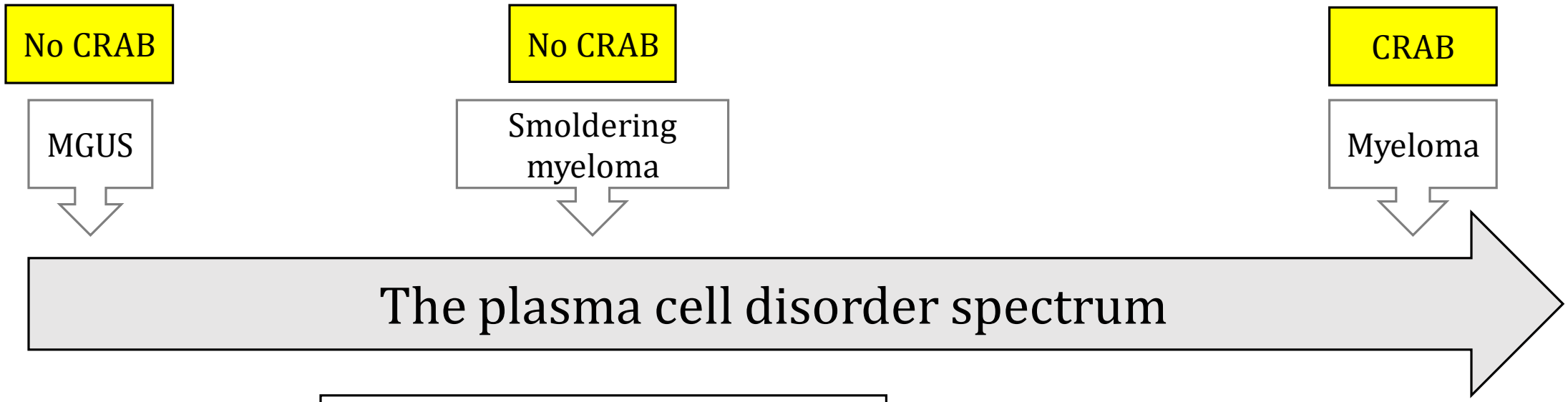
	CRAB	**M protein**	**BM plasma cells**
MGUS	No	<30 g/L	<10%
Myeloma	Yes	Any size!	>10%

Take home message

If the M protein is **>30 g/L**, this is **not MGUS**

If the M protein is **<30 g/L**, this **may still be myeloma**
(*think CRAB!)*

A bit of a more sophisticated view

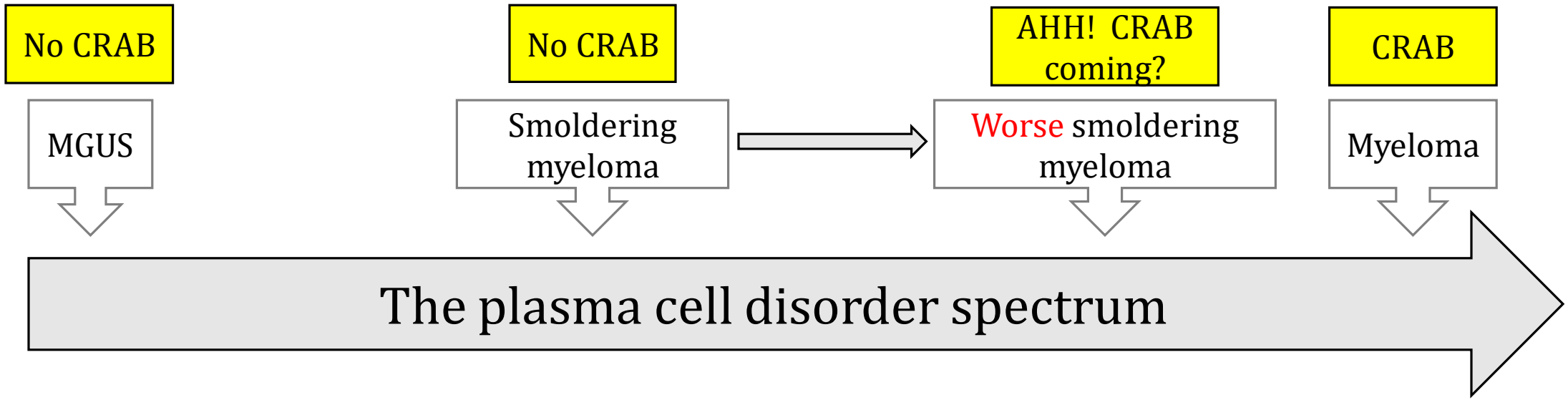


By definition:

- No CRAB
- M protein > 30 g/L **and/or**
- BM plasma cells 10-60%

Higher risk of progression to myeloma, but **we still do not treat**

A bit of a more sophisticated view



- **"Ultra high risk"** smoldering myeloma
- Risk of progression of > 80% over 2 yrs
- Certain defining features = **SLiM criteria**

Nice to know, not need to know

There is a bit more to myeloma than CRAB…

SLiM CRAB

S Bone marrow clonal plasma cells **>Sixty%**

Li **Li**ght chain ratio >100, with involved light chain >100 mg/L

M >1 bone lesion on whole body **M**RI

So high risk for progression, now part of diagnostic criteria for myeloma. **Just treat.**

What is myeloma?

By definition:

- At least one **SLiM CRAB** manifestation
- Bone marrow clonal plasma cells >10%

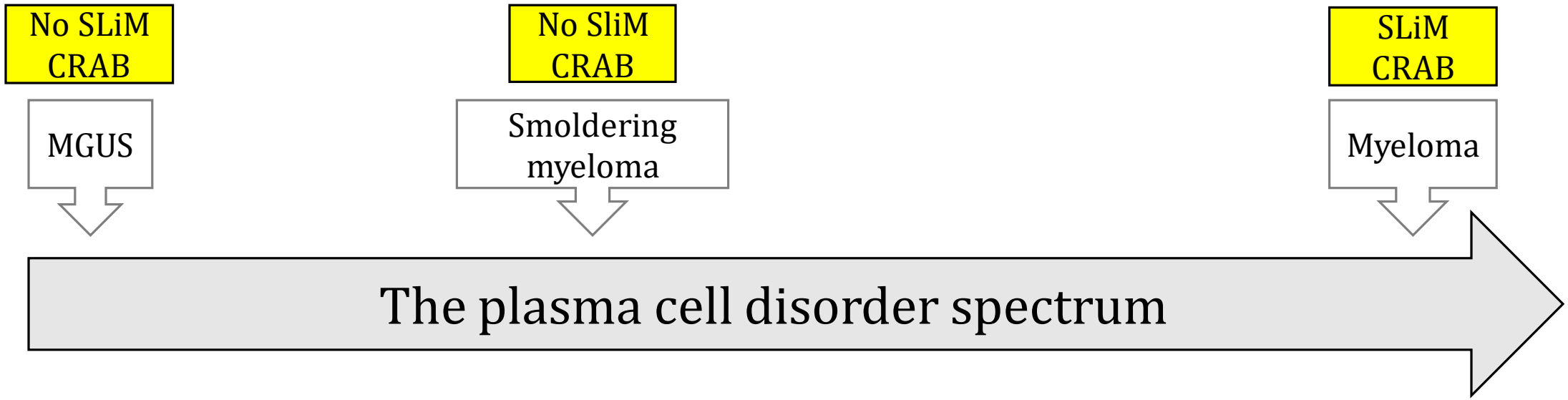
The SLiM criteria in your office

Light chain ratio >100, with involved light chain >100 mg/L

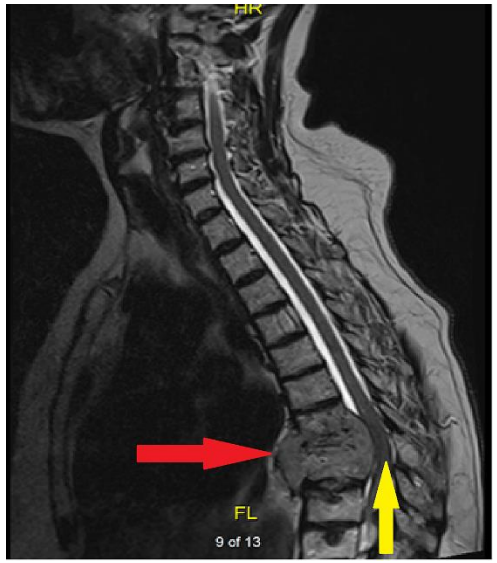
Take home message

When worried about myeloma, *even without CRAB*, pay attention to **very abnormal FLC assays**

The current view



One more plasma cell disorder



Solitary plasmacytoma

Biopsy proven **solitary** lesion with clonal plasma cells

- **NO** other bone lesions
- **NO** bone marrow clonal plasma cells
- **NO** other SLiMCRAB

Treated with **radiation with curative intent**

Back to MGUS, why do we care?

and other lymphoproliferative disorders

MGUS is to myeloma as polyps are to colon cancer!

With a giant **BUT…**

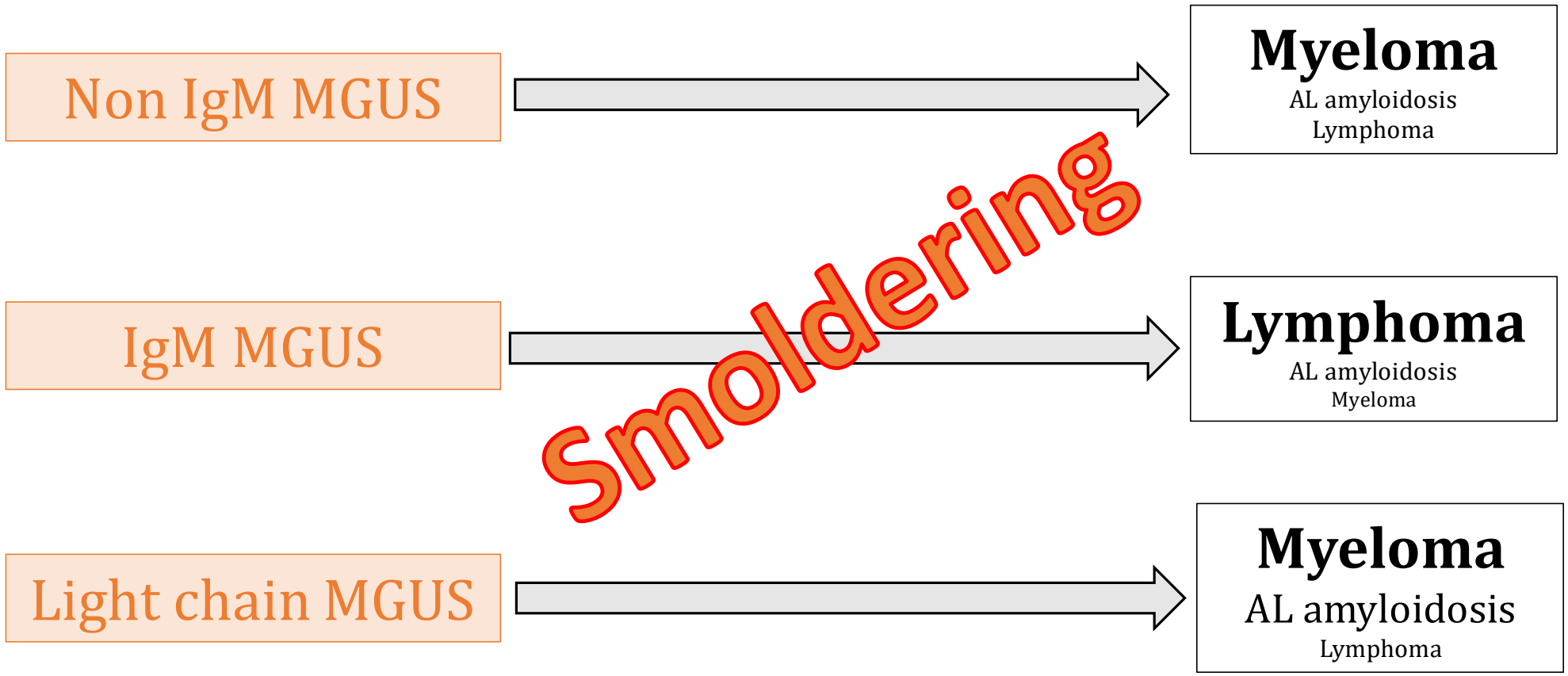
- No evidence for population screening
- Conflicting evidence as to whether following MGUS prevents progression to CRAB or prolongs survival

MGUS classification

67%	Non IgM MGUS	IgG	55%
		IgA	9%
		IgD	<1%
		Biclonal	3%
14%	IgM MGUS		
19%	Light chain MGUS		

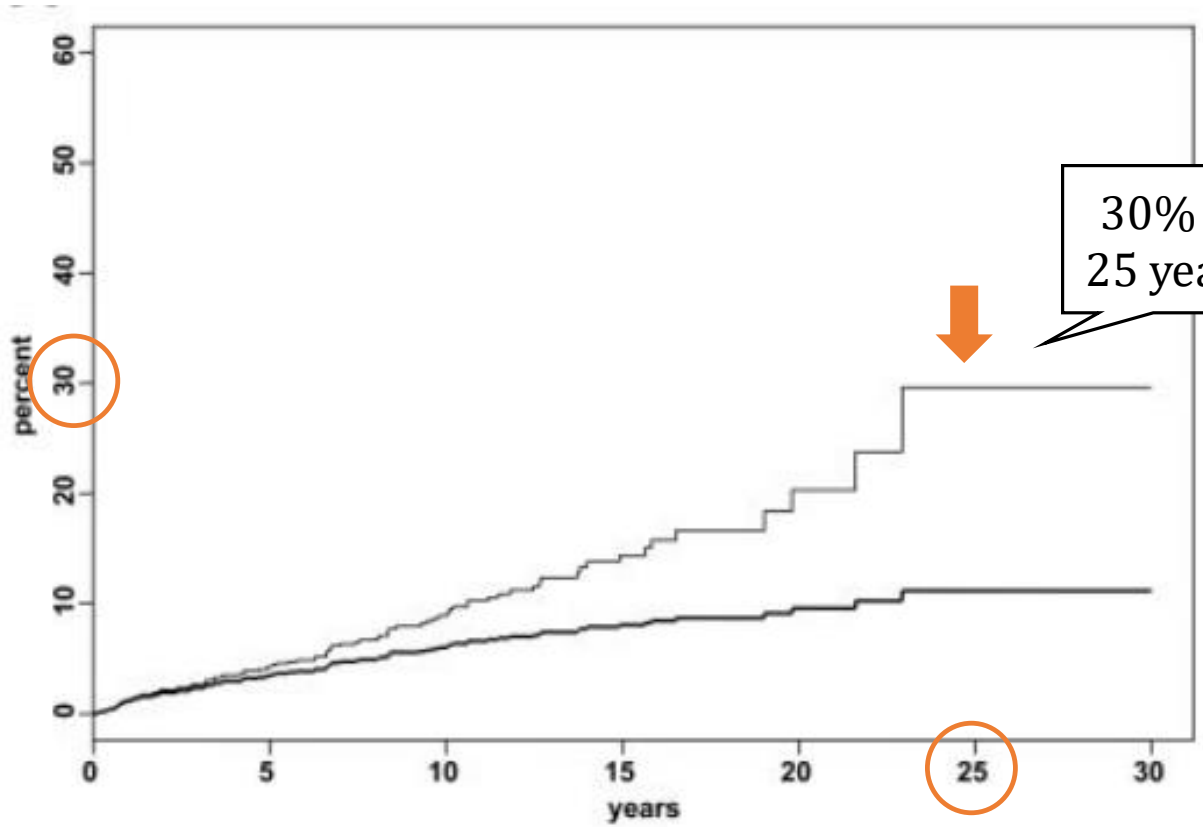
3/4 low risk isotype

MGUS patterns of progression



Risk of MGUS progression

1148 Mayo Clinic MGUS pts followed for 8982 person yrs



30% at 25 years

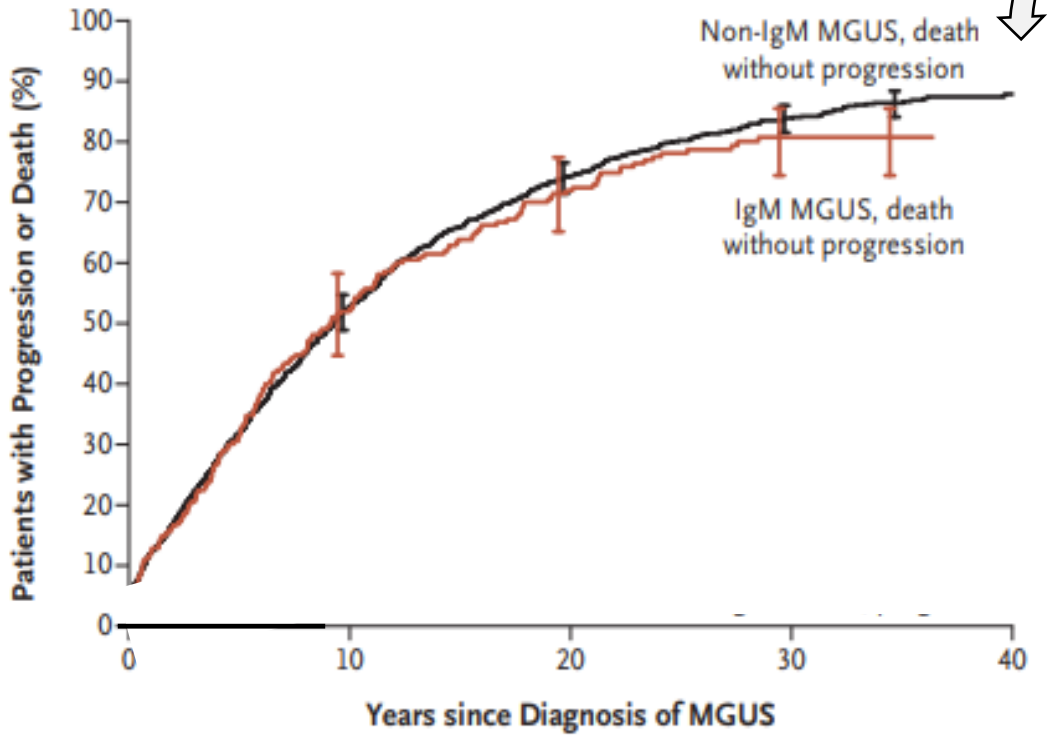
1% per year

But much lower when competing causes of death taken into account:
10% at 25yrs

Rajkumar et al, Blood 2005

Even more reassuring!

1384 Mayo Clinic MGUS pts followed for 14130 person yrs



87% died from other causes

Kyle et al, NEJM 2018

Mayo Clinic MGUS risk stratification

Risk factor
1. Non IgG isotype
2. Amount > 15 g/L
3. Abnormal FLC ratio

Group	RF	Progression at 20 yr	% pts
High	3	58%	4%
High-Int	2	37%	20%
Low-int	1	21%	37%
Low	0	5%	39%

Most pts are pretty low risk!

Rajkumar et al, Blood 2005

So how do we follow*?

Consensus Guidelines on the Diagnosis of Multiple Myeloma and Related Disorders: Recommendations of the Myeloma Canada Research Network Consensus Guideline Consortium

Debra J. Bergstrom,[1] Rami Kotb,[2] Martha L. Louzada,[3] Heather J. Sutherland,[4] Sofia Tavoularis,[5] Christopher P. Venner,[6] for the Myeloma Canada Research Network Consensus Guideline Consortium*

Clinical Lymphoma, Myeloma & Leukemia, Vol. 20, No. 7, e352-67 © 2020

Bloodwork in 6 m, then yearly

*Ahem…although we don't even know if follow-up **prevents CRAB or prolongs survival!**

MGUS diagnosis - not always so benign?

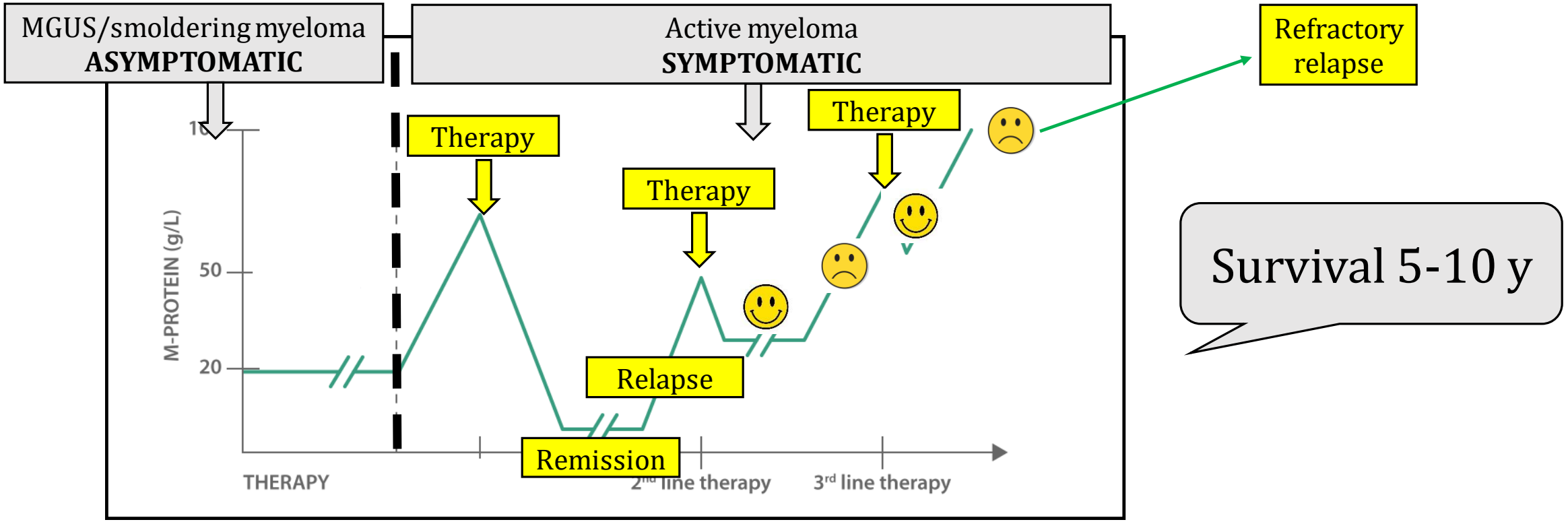
Case 7. Harms of MGUS diagnosis

A 32-year-old woman was incidentally found to have an M-protein after participating in a blood donor screening held at a plasma donation center. She was healthy otherwise and given a diagnosis of MGUS. For 5 years, she was followed annually by her hematologist, and her M-protein remained stable. During the most recent visit, she confided, for the first time, that she was "scared to death" to come to follow-up visits. Every day, she felt as though she was "living on a cliff" and "could fall off anytime." She lived in fear of hearing "the bad news" that she might not be lucky enough to "dodge the bullet" this time.

Go and Rajukumar, Blood 2018

Back to myeloma, how it goes

Treatable but not curable



Survival 5-10 y

Ghandi et al, Leukemia 2019; Rajkumar, AJH 2022

Chemotherapy Protocols

Myeloma

17 protocols

Take home message

For most patients, **MGUS** is a bit of a **nothing**
➡ **elective referral**

Myeloma on the other hand, is **bad**
➡ **urgent referral**

INTERLUDE

COFFEE & TEA

Uncommon stuff,
MGCS & polyclonal hypergammaglobulinemia

Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

Nelson Leung,[1,2] Frank Bridoux,[3] Colin A. Hutchison,[4] Samih H. Nasr,[5] Paul Co… …rmand,[6] Angela Dispenzieri,[2] Kevin W. Song,[7] and Robert A. Kyle,[2] on behalf of th… …nd Monoclonal Gammopathy Research Group

MGRS

Blood. 2012;120(22):4292-4295

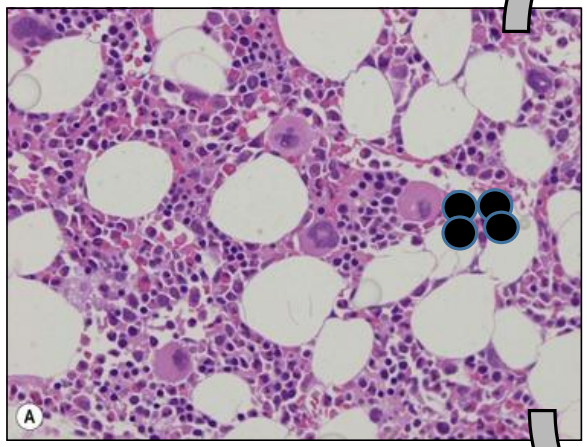
Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications

Jean-Paul Fermand,[1] Frank Bridoux,[2] Angela Dispenzieri,[3] Arnaud Jaccard,[4] Robert A. Kyle,[3] Ne… …Gi…paolo Merlini[6,7]

MGCS

Blood. 2018;132(14):1478-1485

The dangerous small B cell/plasma cell clone



NOT replacing the marrow
NOT filling up lymph nodes
NOT destroying bone
NOT producing a large M protein

INSTEAD, produces a **small nasty** M protein

Causes problems via **various mechanisms**:

- Deposition in tissues
- Autoantibody activity
- Complement or cytokine activation

Example 1, MGRS (NOT myeloma kidney!)

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID)

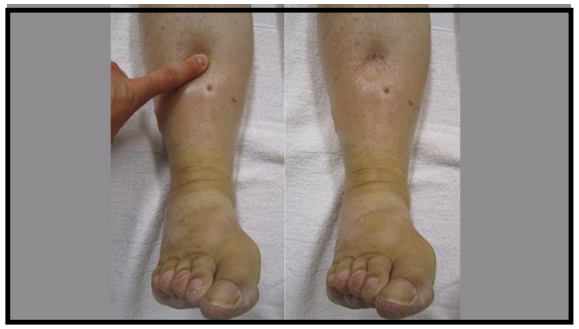
Pathology
- Deposits of intact IgG in glomeruli

Presentation
- Nephrotic or nephritic/nephrotic, rapidly progressive AKI or chronic GN

Treatment
- Clone directed (chemo/immunotherapy)

But of course, much more common = **MGUS plus a common kidney disease**

Example 2, MGCS



Idiopathic systemic capillary leak syndrome (Clarkson's syndrome)

Presentation

- Sick! Anasarca, hypotension, hemoconcentration, hypoalbuminemia
- Then redistribution phase with intravascular volume overload
- Small usually IgGK M protein

Pathophysiology

- Not understood

Treatment

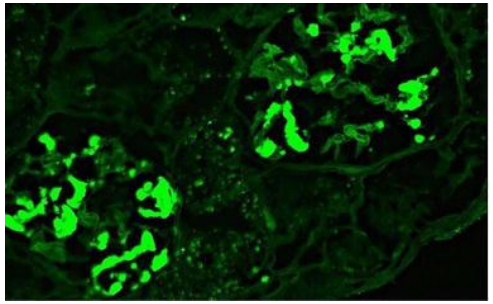
- Supportive (ICU) care acutely
- Then monthly IVIG for prevention

But of course, much more common = **MGUS plus septic schock**

Where does AL amyloidosis fit in?

WITH myeloma = **myeloma plus AL amyloidosis**

WITHOUT myeloma = **MGCS**



What is it anyhow?

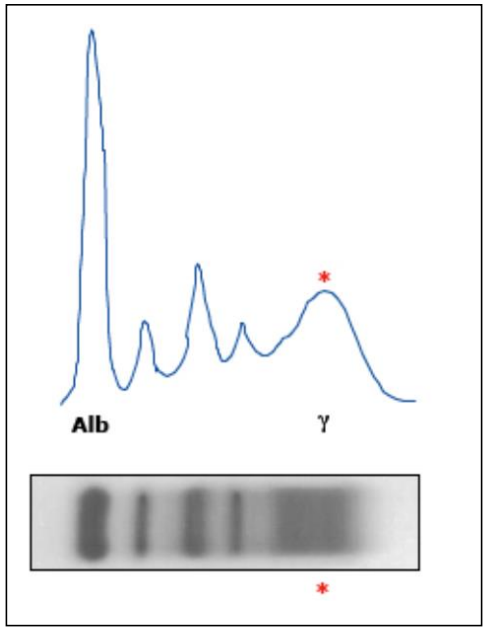
- Plasma cell or lymphoplasmacytic cell disorder
- **Tissue deposition** of **amyloid fibrils** composed of **monoclonal light chains**
- Usually **a small M protein**, often light chain only (usually lambda)
- Leads to **organ dysfunction**, esp. heart, kidneys, nerves
- **BAD** disease!
- Treated with chemo/immunotherapy

Take home message

For patients with M proteins, do a **review of systems**. If there is a weird symptom, consider **MGCS**

The **MGCS** are rare, with myriad signs and symptoms. **Impossible to remember**, just look things up

One slide for polyclonal hypergammaglobulinemia



Another important and useful finding on SPEP

Usually a **physiologic reaction** to liver, autoimmune or inflammatory disease.
Usually **NOT a hematologic problem**

Sometimes a clue to **rare and difficult to diagnose** diseases, eg. EGPA, Castleman's disease

Hard to find a good resource

OK, one more slide

Polyclonal hypergammaglobulinaemia: assessment, clinical interpretation, and management

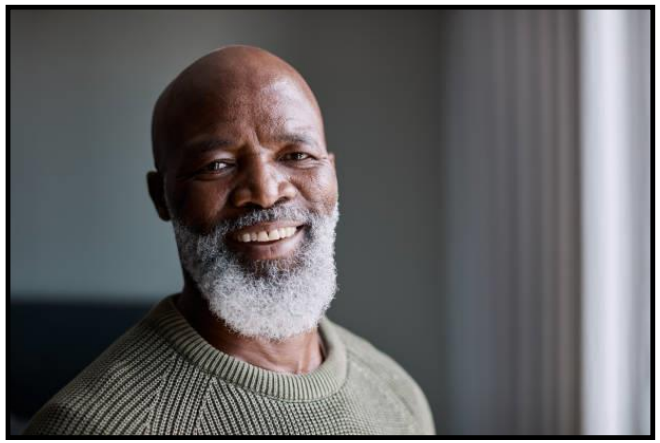
Eric J Zhao, Catherine V Cheng, Andre Mattman, Luke Y C Chen

www.thelancet.com/haematology **Vol 8 May 2021**

INTERLUDE

COFFEE & TEA

Case 1



82 yr old man with OA and chronic hip pain

Presents with fatigue and low mood

Mild anemia, Hb 125 g/L

SPEP **IgGK M protein 3 g/L**

UPEP negative

Rest of CBC normal, Cr normal, Calcium normal

Likely diagnosis?

A. Lymphoma

B. MGUS ✓

C. Myeloma

D. AL amyloidosis

Case 2

70 F with T2 diabetes, obesity, dyslipidemia

Presents with fatigue and acute on chronic back pain

Hb 99, WBC 4.0, plts 145

SPEP **IgA L M protein 29 g/L**

FLC assay K 8 mg/L, L 300 mg/L, **ratio 0.03**

Calcium 2.6 mmol/L, Cr120 umol/L

Likely diagnosis?

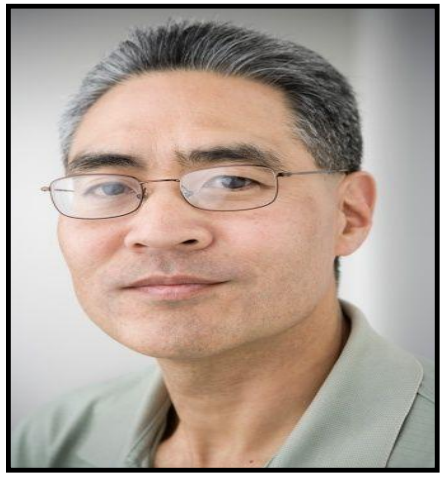
A. Lymphoma

B. MGUS

C. Myeloma 

D. MGRS

Case 3



55 M with well controlled HTN

Presents with fatigue and 2-3 lb weight loss

Hb 89, WBC 3.0, plts 100

SPEP **IgM K M protein 55 g/L**

UPEP negative

Calcium and creatinine normal

Likely diagnosis?

A. Small lymphocytic lymphoma

B. IgM MGUS

C. Myeloma

D. Lymphoplasmacytic lymphoma ✓
(Waldenstrom's macroglobulinemia)

Case 4

Healthy 35 F with no medical problems

Presents with episodic itchy hives, fever & malaise

Hb 112, WBC 8, plts 202

SPEP **IgM K M protein 3 g/L**

UPEP negative

Calcium and creatinine normal

Likely diagnosis?

A. Lymphoma

B. IgM MGUS

C. Myeloma

D. Schnitzler’s syndrome (MGCS) ✓


"That's all Folks!"