«Μονοκλωνική γαμμαπάθεια»
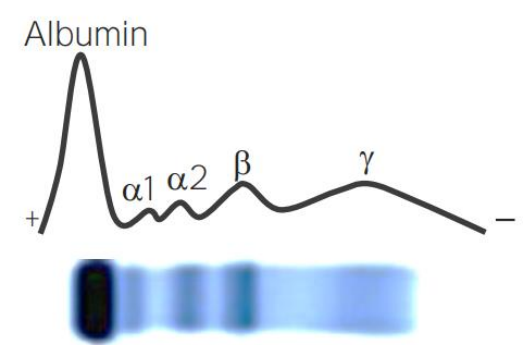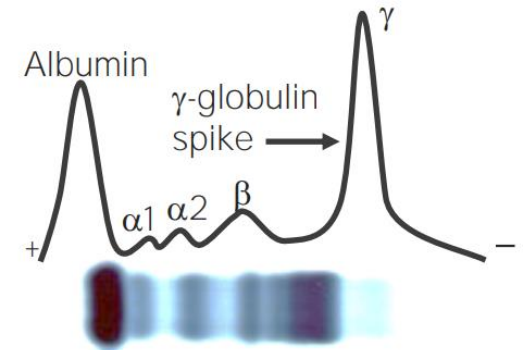
Βασιλική Λαμπροπούλου

Επίκουρη Καθηγήτρια Παθολογίας-Αιματολογίας

Αιματολογικό Τμήμα Παθολογικής Κλινικής

Π.Γ.Ν.Πατρών

Monoclonal gammopathy of undetermined significance (MGUS)

First description in 1960 by Jan Waldenstrom as:

"**essential hyperglobulinemia**" or "**benign monoclonal gammopathy**"

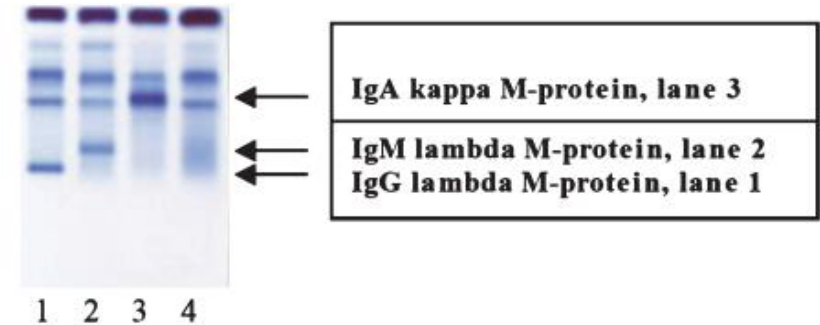A term originally coined by the Mayo Clinic group (Kyle, 1978):

- **monoclonal protein in the serum or urine** of an individual **with no evidence of multiple myeloma, AL amyloidosis, Waldenström macroglobulinemia (WM) or other lymphoproliferative disorders**

M-proteins are frequently identified during investigation of

- **unrelated symptoms**

- **during health screening**

and their identification presents clinicians with the **challenge of ......**

    ...Whom .... And .... How far to investigate?

IgA kappa M-protein, lane 3
IgM lambda M-protein, lane 2
IgG lambda M-protein, lane 1

1 2 3 4

Lane 1 shows an IgG lambda M-protein of 7 g/l

Lane 2 shows an IgM lambda M-protein of 8 g/l

Lane 3 shows an IgA kappa M-protein of 28 g/l

Lane 4 shows normal polyclonal immunoglobulins

MGUS

- MGUS is present **in 3% of the general population >50 years, 5% ≥70 years, 0.3% <50 years**

- **Higher risk** and **earlier age** of onset in **blacks** than in whites

- The median age of MGUS diagnosis is **70 years**

- The **etiology is unclear:** predisposing factors include
    - **family history** of **hematological malignancy**,
    - **immunosuppression**,
    - **radiation exposure** and **pesticides**

Progress in

- …. **biology, epidemiology, disease associations** of MGUS**,**

- **……universal agreement on the criteria for the diagnoses of MGUS and LPMs**

- But… guidelines for initial evaluation and subsequent follow-up of MGUS are less than uniform

MGUS definition

MGUS is a clinically

asymptomatic,

premalignant,

clonal plasma cell disorder

And

is an **obligatory precursor** for several LPMs, including **MM, WM, and AL**

Criteria for diagnosis and risk of progression in MGUS [1]

Subtype of MGUS	Diagnostic criteria	Risk of progression	Pattern of progression
IgM MGUS	All 3 criteria must be met: • Serum IgM monoclonal protein <3 gm/dL • Bone marrow lymphoplasmacytic infiltration <10%* • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	1% per year	Waldenström macroglobulinemia, AL amyloidosis; rarely IgM multiple myeloma
Non-IgM MGUS	All 3 criteria must be met: • Serum monoclonal protein (non-IgM type) <3 gm/dL • Clonal bone marrow plasma cells <10%* • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	0.5% per year	Multiple myeloma, solitary plasmacytoma, AL amyloidosis
Light-chain MGUS	All criteria must be met: • Abnormal FLC ratio (<0.26 or >1.65) • Increased level of involved light chain (increased κ FLC in patients with FLC ratio >1.65 and increased λ FLC in patients with FLC ratio <0.26) • No immunoglobulin heavy-chain expression on immunofixation • Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder • Clonal bone marrow plasma cells <10%* • Urinary monoclonal protein <500 mg per 24 h	0.3% per year	Light-chain multiple myeloma and AL amyloidosis

IgM MGUS has a higher risk of progression than non-IgM and is typically associated with progression to lymphoplasmacytic lymphoma/WM. The risk of progression among patients with IgM MGUS is **2% per year in the first 10** years after diagnosis and **1% per year** thereafter[2]

1. R. Go and V. Rajkumar, Blood 2018

2. Jithma P. Abeykoon et al., Faculty Reviews 2022

Case 1.
Indications for testing and disease associations

- A **75-year-old man** presenting with a **5-day history of headache, persistent cough, severe lower-rib pain and generalized weakness**.

- Physical examination and chest x-ray were unremarkable.

- His laboratory evaluation was remarkable only for **a hemoglobin of 12.5 g/dL** (13.5-16.5).

- Serum protein electrophoresis (SPEP), immunofixation, and free light-chain (FLC) studies revealed a **monoclonal IgGλ of 0.5 g/dL with normal FLC values.**

- The next day, nasal swab showed the presence of influenza A.

- The anemia and rib pains resolved weeks later.

When should testing for M-proteins be carried out?

1. Screening **normal populations for M-proteins** for clinical purposes **is not recommended.**

2. Electrophoresis of serum and urine should always be requested where there is **clinical suspicion of plasma cell dyscrasia/B-cell malignancy**. If the clinical suspicion is strong **despite the absence of a detectable M-protein,** then **immunofixation** should be performed. **SFLC** measurement is required to **detect AL amyloidosis** and **light chain myeloma**.

3. **Electrophoresis of serum and urine should be requested in all patients** with a persistent elevation of **ESR > 30 mm/h**, anaemia, **renal failure** or **hypercalcaemia** with no other obvious explanation.

4. Serum **protein electrophoresis** should perform when there are **abnormally high or low serum levels of total immunoglobulin or individual Ig classes**.

Detailed history and examination
Symptoms and signs and test results commonly associated with myeloma, lymphoma or AL amyloid

Table X. Symptoms and signs and test results commonly associated with myeloma, lymphoma or AL amyloidosis.

Myeloma	Lymphoma/LPD	AL amyloidosis
Hypercalcaemia	Lymphadenopathy	Macroglossia
Renal failure	Hepatosplenomegaly	Unexplained heart failure
Anaemia	Hyperviscosity (especially if IgM) M-protein	Peripheral neuropathy
Bone pain/lesions	Pancytopenia	Carpal tunnel syndrome
Hyperviscosity	Symptoms e.g. night sweats, fever, weight loss	Nephrotic syndrome

What are the nonmalignant diseases associated with monoclonal gammopathy?

- MGUS has been reported to **be associated with >130 different diseases** in addition to progression to malignancy.

- Because of the **high prevalence of MGUS in the general population, most of these reported** associations are likely **coincidental**.

- Some associations have been verified and are now considered to be **causally related to MGUS.**

Disease Associations With Monoclonal Gammopathy of Undetermined Significance: A Population-Based Study of 17,398 Patients

JOHN P. BIDA, MA; ROBERT A. KYLE, MD; TERRY M. THERNEAU, PhD; L. JOSEPH MELTON III, MD; MATTHEW F. PLEVAK, MS; DIRK R. LARSON, MS; ANGELA DISPENZIERI, MD; JERRY A. KATZMANN, PhD; AND S. VINCENT RAJKUMAR, MD

Objective: the **association of MGUS with all diseases** in a population-based cohort of **17,398 patients**, all of whom were uniformly tested for the presence or absence of MGUS.

Patients and Methods: Among **17,398 samples tested, 605 cases of MGUS and 16,793 negative** controls were identified, between **January 1, 1975, and May 31, 2006**, for a total of 422,663 person-years of observations

Results: We confirmed a **significant association in 14 (19%) of 75 previously reported disease associations with MGUS,** including **vertebral and hip fractures and osteoporosis**.

Conclusion: These results have major implications both for **confirmed associations** and for 61 diseases in which the association with **MGUS is likely coincidental.**

TABLE 1. Previously Published Disease Associations in Which a Significant Disease Association With MGUS Was Confirmed Among Olmsted County, Minnesota, Residents[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Risk ratio (95% CI)	P value[c]
Macroglobulinemia[9,19,20]	5	55.1	1	0.6	96.2 (11.0-836.5)	<.001
Multiple myeloma[9]	29	257.4	19	7.9	32.6 (18.1-58.7)	<.001
Plasma cell proliferative disorder[9]	11	87.1	9	3.1	28.0 (11.4-68.7)	<.001
Amyloidosis[9]	7	85.2	18	11.8	7.2 (3.0-17.4)	<.001
CIDP[21,22]	2	14.9	8	2.5	5.9 (1.2-28.4)	.03
Liver transplant[23]	2	13.9	10	2.6	5.4 (1.2-25.3)	.03
Kidney transplant[24-27]	5	34.6	38	9.8	3.5 (1.4-9.1)	.01
Lymphoproliferative disease[28]	17	161.2	105	48.0	3.4 (2.0-5.6)	<.001
Autonomic neuropathy[29]	5	35.8	39	11.0	3.2 (1.3-8.3)	.01
Vertebral fracture[17]	46	511.1	478	263.9	1.9 (1.4-2.6)	<.001
Hip fracture[17]	36	581.6	388	377.1	1.5 (1.1-2.2)	.01
Hypercalcemia[30]	40	297.5	736	214.9	1.4 (1.0-1.9)	.05
Osteoporosis[31]	153	1701.1	3013	1407.7	1.2 (1.0-1.4)	.02
Urticaria[32-34]	20	144.8	1003	242.9	0.6 (0.4-0.9)	.02

[a] CI = confidence interval; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; MGUS = monoclonal gammopathy of undetermined significance.
[b] Rates per 100,000 person-years; age and sex adjusted.
[c] Unadjusted P values are reported.

TABLE 4. Top 20 Previously Unpublished Associations Among Olmsted County, Minnesota, Residents With MGUS, by Hazard Ratio With P<.05 and 10 or More Total Cases and Controls in Systematic Analysis of Diagnostic Codes[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Relative risk (95% CI)	P value[c]
Benign cervix neoplasm	2	26.1	8	2.2	11.8 (2.5-56.8)	.002
Esophageal bleeding	3	21.0	8	2.2	9.7 (2.5-37.3)	.001
Peritoneum cyst	4	28.3	14	3.2	8.8 (2.8-27.2)	<.001
Sural phlebitis	4	29.3	13	3.3	8.8 (2.8-27.3)	<.001
Tympanosclerosis	3	22.6	11	2.7	8.4 (2.3-30.7)	<.001
Popliteal artery embolism	3	38.1	7	4.9	7.8 (2.0-30.7)	.003
Inhalation of fumes	5	39.1	20	5.0	7.8 (2.9-21.0)	<.001
Open wound, buttock	3	21.5	10	2.8	7.7 (2.1-28.7)	.002
Neck injury, musculoskeletal	2	15.0	9	2.0	7.4 (1.6-35.1)	.01
Fracture plate removal	2	14.7	9	2.1	7.1 (1.5-33.8)	.01
Angiomyolipoma	2	13.8	8	1.9	7.1 (1.5-34.4)	.01
Marginal gingivitis	3	23.7	14	3.3	7.1 (2.0-25.1)	.002
Femoral artery embolism	3	26.7	9	3.8	7.1 (1.9-26.6)	.004
Clavicle fracture, acromial end	3	24.9	14	3.5	7.0 (2.0-24.8)	.002
Bone marrow hyperplasia	3	27.5	9	4.0	6.9 (1.8-25.8)	.004
Ruptured ligament, shoulder	2	13.8	8	2.0	6.9 (1.4-33.0)	.02
Vitelliform dystrophy	3	24.9	10	3.7	6.7 (1.8-24.7)	.004
Postvagotomy syndrome	2	13.9	8	2.1	6.6 (1.4-31.9)	.02
Pelvolithiasis	3	21.6	13	3.2	6.6 (1.9-23.7)	.003

TABLE 2. Previously Published Disease Associations That Were Not Confirmed Among Olmsted County, Minnesota, Residents With MGUS[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Risk ratio (95% CI)	P value[c]
Infections and parasitic diseases						
Chronic hepatitis[35]	4	27.85	46	11.23	2.48 (0.89-6.94)	.08
Cytomegalovirus infection (includes congenital)[36]	1	7.31	13	3.83	1.91 (0.25-14.73)	.54
Epstein-Barr infection[37]	0	0	8	1.98	...	>.99
Hepatitis C[35,38,39]	3	21.39	42	12.02	1.78 (0.55-5.77)	.34
Infectious pneumonitis[40]	91	796.01	1863	706.73	1.13 (0.91-1.39)	.27
Pulmonary tuberculosis[41]	1	8.98	14	5.96	1.51 (0.2-11.56)	.69
Sarcoidosis[42]	3	24.75	68	16.16	1.53 (0.48-4.89)	.47
Neoplasms						
Acute leukemia[43]	1	7.54	3	0.94	8.05 (0.81-80.3)	.08
Chronic lymphocytic leukemia[5,9,44]	6	53.59	115	48.44	1.11 (0.49-2.52)	.81
Hairy cell leukemia[45]	1	8.64	9	3.69	2.34 (0.29-18.66)	.42
Colon cancer[46]	20	246.43	288	193.08	1.28 (0.81-2.01)	.29
Sézary syndrome[47,48]	1	7.56	10	3.18	2.38 (0.3-18.81)	.41
Thymoma[49]	0	0	8	2.88	...	>.99
Endocrine, nutritional, and metabolic diseases						
AIDS[50,51]	0	0	2	0.55	...	>.99
C1 esterase inhibitor deficiency[32,52]	0	0	1	0.23	...	>.99
Diabetic neuropathy[53]	28	243.7	559	223.16	1.09 (0.75-1.6)	.65
Hashimoto thyroiditis[54]	10	76.42	381	87.01	0.88 (0.47-1.65)	.69
Hemosiderosis[55]	1	7.11	17	4.78	1.49 (0.2-11.27)	.71
Hyperparathyroidism[56-60]	9	72.34	184	65.14	1.11 (0.57-2.17)	.76
Xanthogranuloma[61-63]	1	7.28	7	1.64	4.44 (0.53-36.84)	.17
Xanthoma[61]	1	7.34	29	6.98	1.05 (0.14-7.76)	.96

John P. Bida et al, Mayo Clin Proc. 2009

Diseases of blood and blood-forming organs						
Lupus, anti-inhibitor/anticoagulants[64-66]	0	0	23	7.85	...	>.99
Pernicious anemia[40]	8	84.64	147	80.14	1.06 (0.52-2.16)	.88
Red cell aplasia[6,7,68]	0	0	1	0.35	...	>.99
Refractory anemia[69]	8	104.86	74	54.04	1.94 (0.93-4.04)	.08
Thromboembolism[70,71]	32	349.75	599	334.94	1.04 (0.73-1.49)	.81
von Willebrand disease[72]	0	0	2	0.51	...	>.99
Diseases of the nervous system and sensing organs						
Cerebellar ataxia[73]	6	64.71	54	29.6	2.19 (0.94-5.1)	.07
Demyelinating disease (CNS)[74]	3	22.2	35	8.11	2.74 (0.84-8.98)	.10
Gravis myasthenia[49]	1	7.49	18	5.63	1.33 (0.18-10.04)	.78
Multiple system atrophy (CNS) + MND[75]	1	9.47	30	13.84	0.68 (0.09-5.03)	.71
Muscular atrophy	6	45.96	84	27.25	1.69 (0.73-3.88)	.22
Peripheral neuropathy[3,29,76]	68	672.56	1389	652.87	1.03 (0.81-1.32)	.81
Sclerosis + MND[75,77,78]	0	0	19	6.91	...	>.99
Diseases of the digestive system						
Chronic active liver disease[79]	0	0	11	2.87	...	>.99
Cirrhosis[80,81]	6	45.89	78	25.46	1.8 (0.78-4.15)	.17
Liver disease[79,81]	4	29.72	73	22.41	1.33 (0.48-3.64)	.58
Diseases of the genitourinary system						
Proliferative glomerulonephritis[82]	1	7.46	8	2.53	2.95 (0.36-23.91)	.31
Diseases of the skin and subcutaneous tissue						
Angioneurotic edema[6]	1	9.77	18	4.84	2.02 (0.27-15.25)	.50
Dermal mucinosis[6]	1	6.93	31	7.85	0.88 (0.12-6.5)	.90
Erythematosus lupus[65,83,84]	1	6.96	46	10.99	0.63 (0.09-4.61)	.65
Psoriasis[85]	20	143.06	636	157.73	0.9 (0.58-1.42)	.67
Pustular subcorneal dermatosis[86-89]	0	0	6	1.74	...	>.99
Myxedematous lichen[90,91]	1	6.93	31	7.85	0.88 (0.12-6.5)	.90
Pyoderma[92-95]	1	7.87	46	11.17	0.7 (0.1-5.13)	.73
Pyoderma gangrenosum[93]	0	0	2	1.2	...	>.99

John P. Bida et al, Mayo Clin Proc. 2009

TABLE 2. Continued[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Risk ratio (95% CI)	P value[c]
Diseases of the musculoskeletal system and connective tissue						
Ankylosing spondylitis[40,96,97]	1	7.53	35	8.91	0.84 (0.12-6.19)	.87
Connective tissue disorders[98]	27	192	547	139.55	1.38 (0.93-2.03)	.11
Connective tissue disorders except RA[98]	3	20.81	85	20.83	1.0 (0.31-3.17)	>.99
Polymyositis[99,100]	1	9.68	9	4.42	2.19 (0.27-17.5)	.46
RA[98]	24	170.33	468	119.26	1.43 (0.95-2.16)	.09
Scleredema[101-103]	0	0	3	0.72	...	>.99
Scleroderma[98]	1	7.05	31	7.07	1.0 (0.14-7.35)	>.99
Septic arthritis[105,106]	1	8.66	18	7.23	1.2 (0.16-9.03)	.86
Seronegative polyarthritis[107]	2	15.85	47	16.19	0.98 (0.24-4.05)	.98
Sjögren syndrome[108]	3	21.67	56	15.93	1.36 (0.42-4.37)	.61
Symptoms, signs, and ill-defined conditions						
Antibody-antigen reactions (antinuclear antibodies)[98]	1	6.99	78	20.28	0.34 (0.05-2.48)	.29
Fracture long bone[17,109]	120	1055.44	2658	973.76	1.08 (0.90-1.30)	.39
Hyperlipoproteinemia[110]	2	15.08	96	23.64	0.64 (0.16-2.59)	.53
Bone marrow/peripheral blood stem transplant[111]	0	0	10	2.54	...	>.99
HIV positive[112,113]	0	0	3	0.75	...	>.99

[a] CI = confidence interval; CNS = central nervous system; HIV = human immunodeficiency virus; MGUS = monoclonal gammopathy of undetermined significance; MND = motor neuron disease; RA = rheumatoid arthritis.

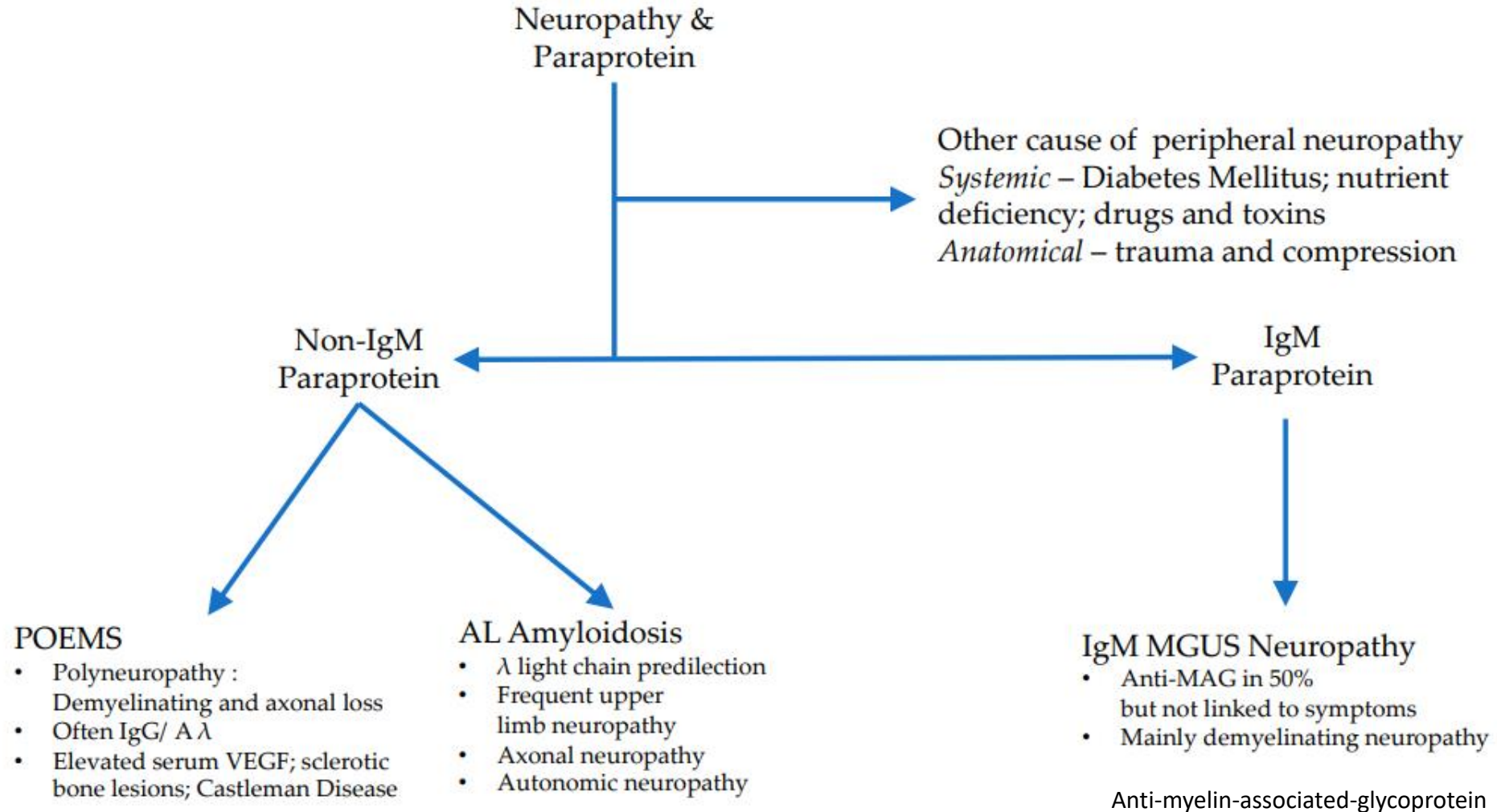[b] Rates per 100,000 person-years; age and sex adjusted.

[c] Unadjusted P values are reported.

John P. Bida et al, Mayo Clin Proc. 2009

Monoclonal gammopathies of (possible) clinical significance but low malignant potential

Term	Organ	Clinical settings, comment
MGRS	Renal	Renal lesions currently incorporated under monoclonal gammopathy of renal significance, including proliferative glomerulonephritis[133]
MGBS	Bone	Acute osteoporosis and osteoporotic fractures
MGDS	Skin	Cryoglobulin vasculitis, Schnitzler syndrome, necrobiotic xanthogranuloma, scleromyxedema, POEMS, pyoderma gangrenosum
MGNS	Neuropathies	Spectrum of neuropathies with MGUS

MGBS, monoclonal gammopathy of bone significance; MGDS, monoclonal gammopathy of dermal significance; MGNS, monoclonal gammopathy of neuropathic significance; MGRS, monoclonal gammopathy of renal significance; POEMS, polyneuropathy, organomegaly, endocrinopathy, M spike, and Skin changes syndrome.

An algorithmic approach to the initial investigation of neuropathy in association with a monoclonal paraprotein

Neuropathy & Paraprotein

Other cause of peripheral neuropathy
Systemic – Diabetes Mellitus; nutrient deficiency; drugs and toxins
Anatomical – trauma and compression

Non-IgM Paraprotein

IgM Paraprotein

POEMS
- Polyneuropathy : Demyelinating and axonal loss
- Often IgG/ A λ
- Elevated serum VEGF; sclerotic bone lesions; Castleman Disease

AL Amyloidosis
- λ light chain predilection
- Frequent upper limb neuropathy
- Axonal neuropathy
- Autonomic neuropathy

IgM MGUS Neuropathy
- Anti-MAG in 50% but not linked to symptoms
- Mainly demyelinating neuropathy

Anti-myelin-associated-glycoprotein

Recommendations

ALERT

The finding of an M-protein in any patient with **polyneuropathy, signs of systemic vasculitis or evidence of cardiac, renal or hepatic abnormalities** and no other explanation should alert the physician to **look for an M protein-related disorder**.

Case 2. Extent of evaluation

A **78-year-old woman** presented chronic **progressive right-shoulder pain.**

Shoulder x-ray: advanced **degenerative arthritis and no lytic lesion**.

Laboratory tests:

- normal CBC, calcium, and creatinine,

- but **total protein was elevated at 8.7 g/dL (6.3-7.9)**

- **IgGκ M-protein of 1.7 g/dL, κ FLC of 8.61 mg/dL**, λ FLC of 0.63 mg/dL, and **κ/λ ratio of 13.67** (0.26-1.65).

Because the M-protein and FLC were substantially elevated, additional work-up was performed.
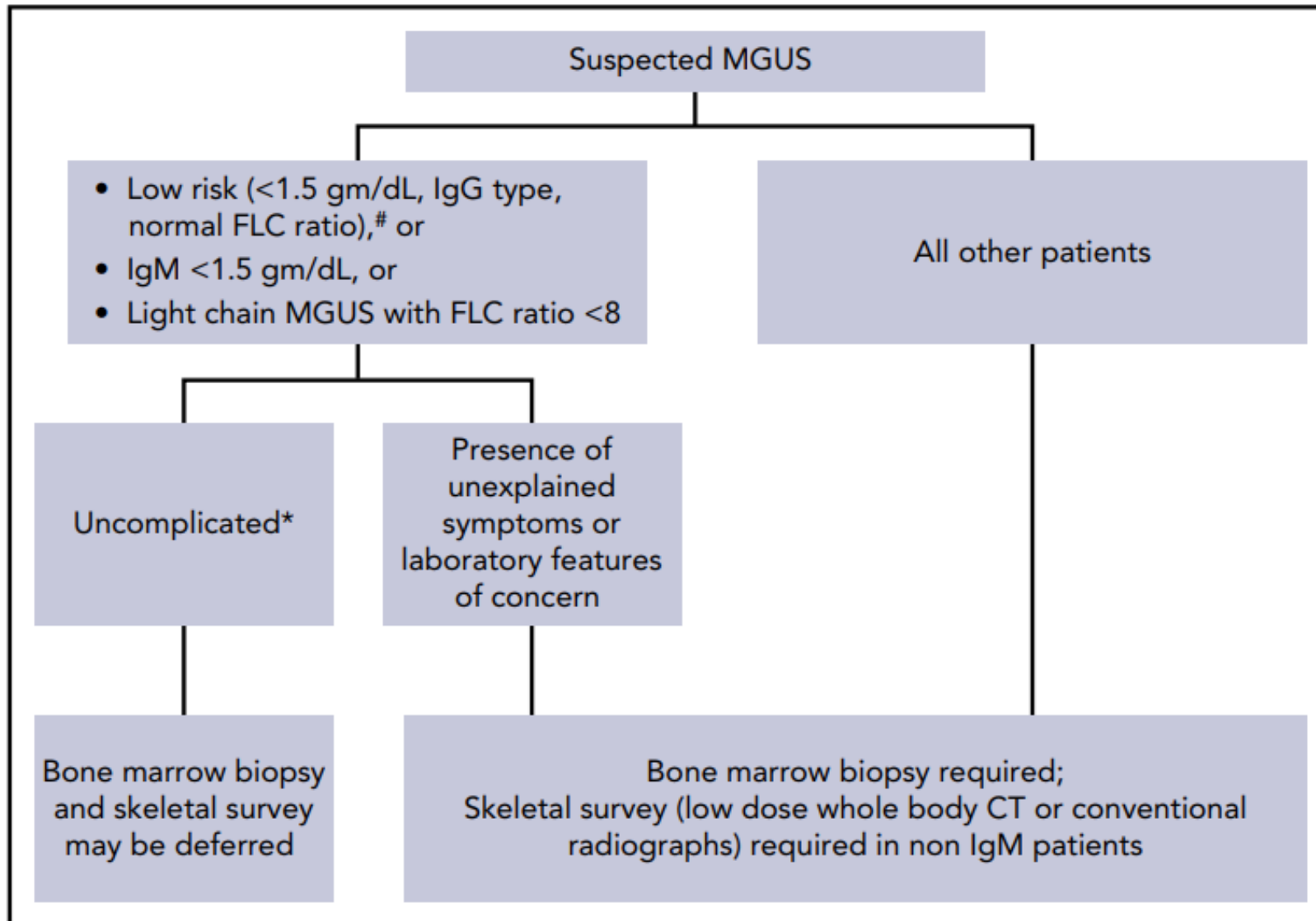
- **A bone marrow biopsy showed 6% κ-restricted** plasma cells.

- A low-dose **whole-body computed tomography (CT) scan did not show lytic lesions.**

She was diagnosed with MGUS

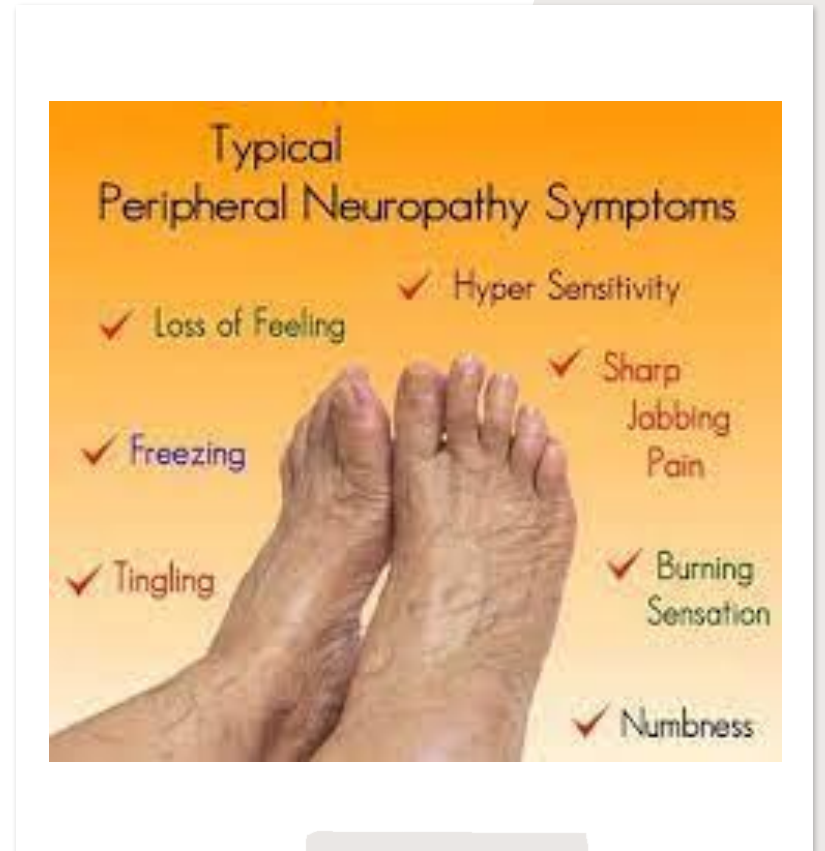When do we perform skeletal imaging and bone marrow biopsy?

Suggested algorithm for bone marrow biopsy and skeletal imaging in patients with MGUS

*No unexplained symptoms or laboratory features concerning for serious plasma cell disorder

R. Go and V. Rajkumar, Blood 2018

Case 3. Follow-up

- **A 70-year-old man was diagnosed with IgGk MGUS 10 years ago during the evaluation of sensory neuropathy.**

- At diagnosis, the serum **M-protein was 0.5 g/dL**

- On repeat testing, the **M-protein was 0.7 g/dL**

- Blood tests showed **normal CBC, calcium, and creatinine levels**.

- FLC studies were performed for the first time and showed κ 2.6 mg/dL, λ 1.8 mg/dL, and **κ/λ ratio of 1.44**

Typical Peripheral Neuropathy Symptoms
- Loss of Feeling
- Hyper Sensitivity
- Freezing
- Sharp Jabbing Pain
- Tingling
- Burning Sensation
- Numbness

What is the evidence for MGUS follow-up?

- The purpose of follow-up in MGUS is to **detect early progression of MGUS into LPM → major complications will be minimized and survival prolonged** because of the initiation of treatment.

- **2 population-based studies** showing **better OS** among **MM patients who had an MGUS diagnosis or follow-up prior to the discovery of MM.**

- In 1 study, the rates **of acute kidney injury, fracture, and hypercalcemia were also decreased.**
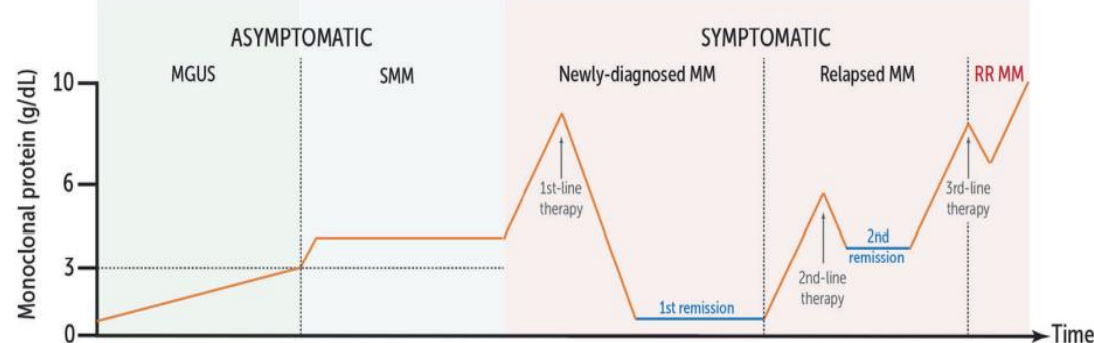
Who do we follow and for how long?

MGUS follow-up recommendations from clinical practice guidelines

MGUS risk/recommended tests	UK Myeloma Forum/Nordic Study Group (2009)[14]	International Expert Consensus (2010)[16]	International Myeloma Working Group (2010)[15]	European Myeloma Network (2014)[17]
Low-risk MGUS (IgG, <1.5 gm/dL, and normal FLC ratio)	First year, every 3-4 mo; then every 6-12 mo if stable	First 2 y, every 4-6 mo; then every 6-24 mo	At 6 mo; then every 2-3 y if stable	At 6 mo; then every 1-2 y if stable or no follow-up
All other MGUS	At least every 3-4 mo	First 2 y, every 4-6 mo; then every 6-24 mo	At 6 mo; then every year if stable	At 6 mo; then every year thereafter
Life expectancy <5 y	Can consider discontinuing follow-up	Not mentioned	Not mentioned	No follow-up
Recommended tests	Quantification of M-protein Serum urea nitrogen CBC Calcium Creatinine Electrolytes Immunoglobulin levels	Quantification of M-protein	Quantification of M-protein CBC	Quantification of M-protein CBC Calcium Creatinine

Case 4. Progression

| Disease stage	MGUS	SMM	Active MM
Serum M-protein	<3 g/dL	≥3 g/dL	≥1 myeloma defining events + (1) or (2):
Urine M-protein	N/A	≥500 mg/day	**End-organ damage (CRAB):** any one of • Hypercalcemia, renal insufficiency, anemia, bone lesions
% BM plasma cells	<10%	10-60%	**Biomarkers of malignancy:** • ≥60% clonal BM plasma cells, • Serum involved/uninvolved free light chain ratio ≥100 • >1 focal lesion on MRI ≥5mm in size
Myeloma defining events	Absence of myeloma defining events or amyloidosis		(1) Clonal bone marrow plasma cells ≥10% or
Progression risk	1% per year	10% per year (1st 5y) 3% per year (next 5y)	(2) Biopsy proven plasmacytoma

- A 50-year-old man presented **with anemia and new onset of severe back pain.**

- He had been diagnosed with **MGUS 9 years ago** with a serum **monoclonal IgG κ of 1.7 g/dL**.

- He was followed **annually**, and the M-protein between **1.6 and 1.9 g/dL**.

- Over the last 2 years, there was a **gradual rise** in **M-protein to 2.5 g/dL**, a **further increase in M-protein to 3.2 g/dL.**

- Serum FLC assay showed κ 23.6 mg/dL, λ 1.0 mg/dL, and **FLC ratio of 23.6**.

- **Skeletal survey detected multiple lytic lesions and pathologic vertebral fractures.**

- **Bone marrow biopsy revealed 50% κ-restricted plasma cells**

When should we suspect progression to an LPM?

Progression should be considered

- **if >25% increase in PP levels occurs over a 3-month period** (minimum 0.5 g/dL) and in the

- **presence of any unexplained signs and symptoms --> bone marrow or tissue biopsy and imaging studies**

- **Current diagnostic criteria for MM have been updated to allow a diagnosis to be made prior to end-organ damage**
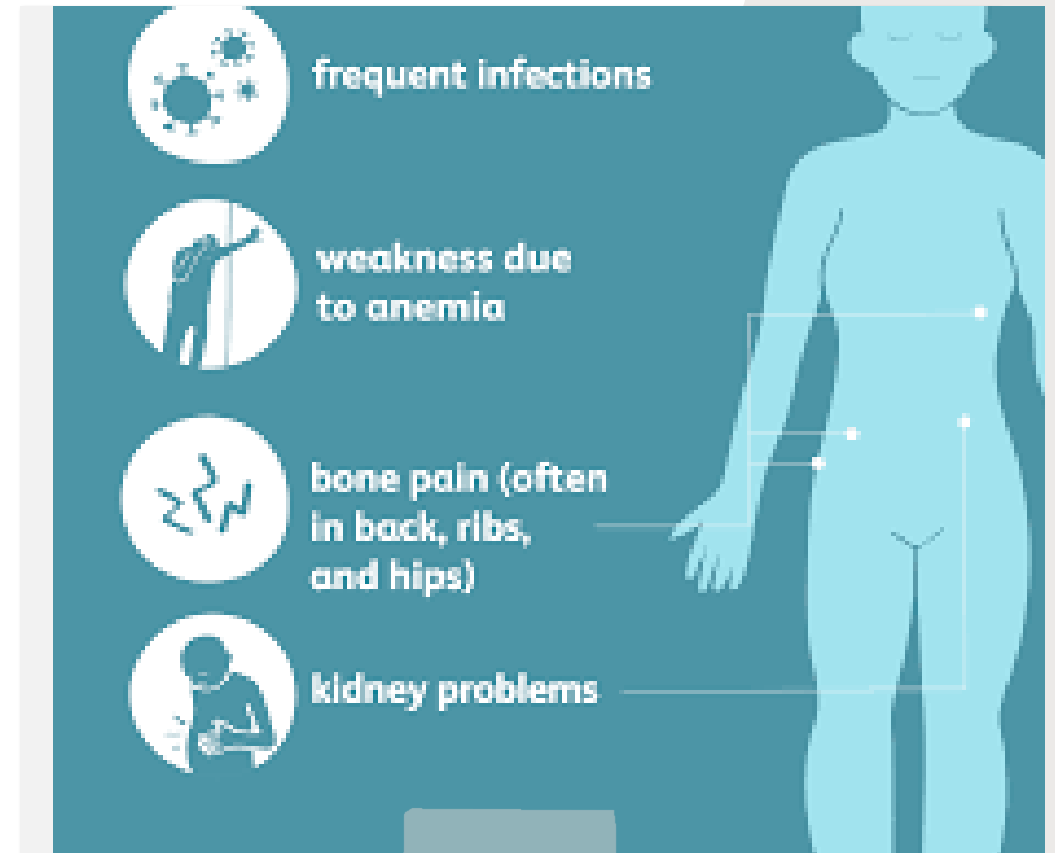
Clinical and laboratory findings of malignant progression

Clinical signs/symptoms (unexplained)

1. Anemia
2. Cardiomyopathy (restrictive)
3. Diarrhea
4. Fracture
5. Hepatomegaly
6. Hypercalcemia
7. Hyperviscosity (in the setting of IgM M-protein)
8. Intestinal pseudo-obstruction
9. Lytic lesion
10. Macroglossia
11. Nephrotic syndrome
12. Neuropathy (autonomic, sensory, or motor)
13. Purpura
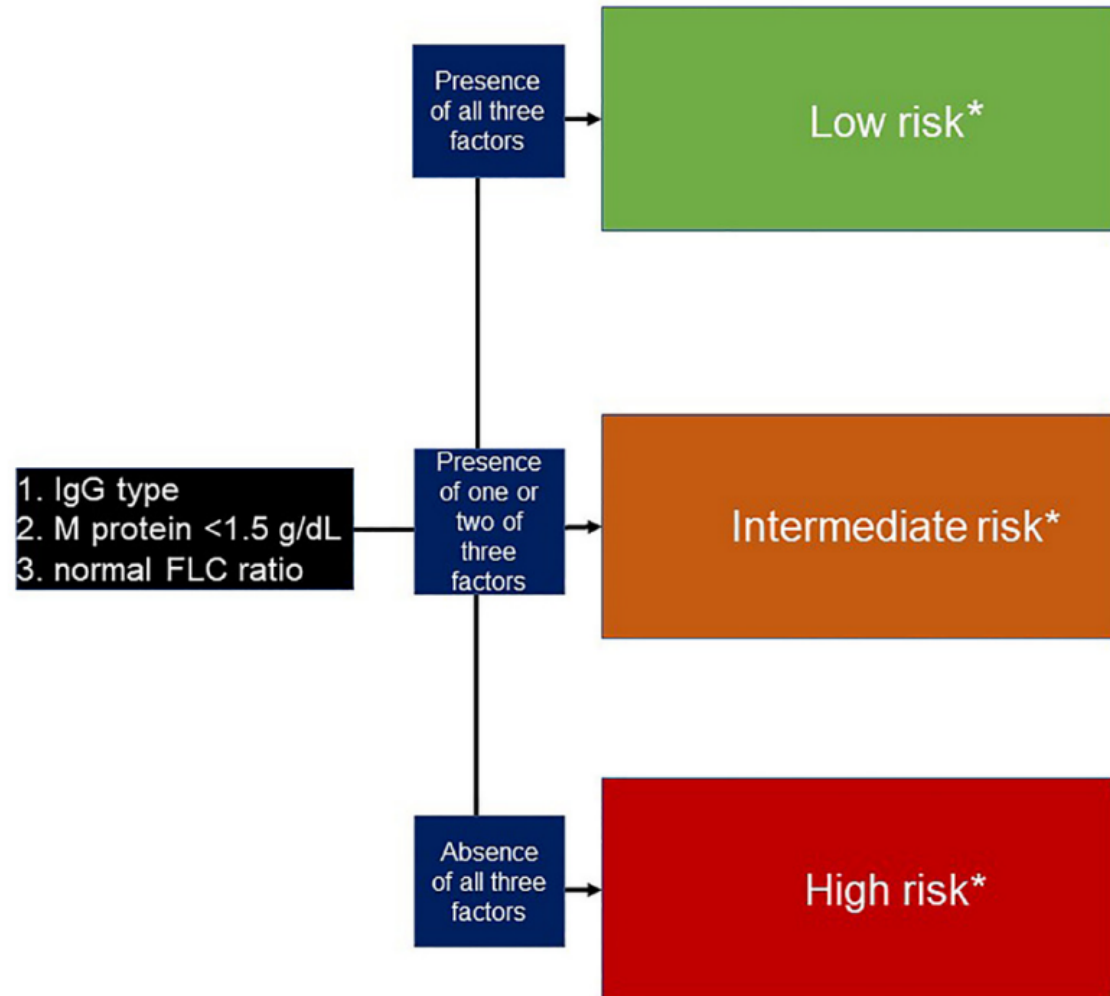14. Renal insufficiency

Monoclonal protein studies

1. Serum M-protein: IgG or IgA ≥3.0 g/dL
2. Urine M-protein ≥ 500 mg in 24 h
3. Serum κ or λ free light chain ≥100 mg/dL and involved/uninvolved FLC >100
4. 50% increase in serum monoclonal protein (absolute increase of ≥0.5 g/dL)

Mayo MGUS risk stratification

The three major risk factors for the progression of MGUS are an
- abnormal serum FLC ratio
- non-IgG MGUS
- high serum M protein level (≥1.5 g/dL)

- **Low risk: 5%** risk of progression in 20 years
- **Intermediate risk: 20%** risk of progression in 20 years
- **High risk: 60%** risk of progression in 20 years

Presence of all three factors → Low risk*

1. IgG type
2. M protein <1.5 g/dL
3. normal FLC ratio

Presence of one or two of three factors → Intermediate risk*

Absence of all three factors → High risk*

Case 5.
Screening for monoclonal gammopathy in asymptomatic patients

- A 61-year-old man was referred to hematology because of a **strong family history of MM**.

- His mother was diagnosed with active MM at the age of 70 and died 8 years later, and his sister was found to have the same diagnosis just 3 months before the visit.

- **SPEP and FLC performed, and no M-protein was detected.**

- **Current practice guidelines do not recommend routine screening for MGUS in the general population** because of the lack of proven benefit and absence of curative or preventive therapy.

Diagnosis of MGUS and follow up

All patients require **history and examination**,

- **full blood count**,

- **renal function,**

- **serum calcium,**

- **total protein,**

- **serum, and urine protein electrophoresis with immunofixation and serum free light chains**

- **BM aspirate and trephine biopsy and**

- **skeletal survey (or CT chest abdomen and pelvis in IgM MGUS)** should be performed when serum **PP ≥ 1.5 g/dL, abnormal SFLC ratio (>10 or <0.10)**

Maciocia et al, Hematological Oncology. 2017
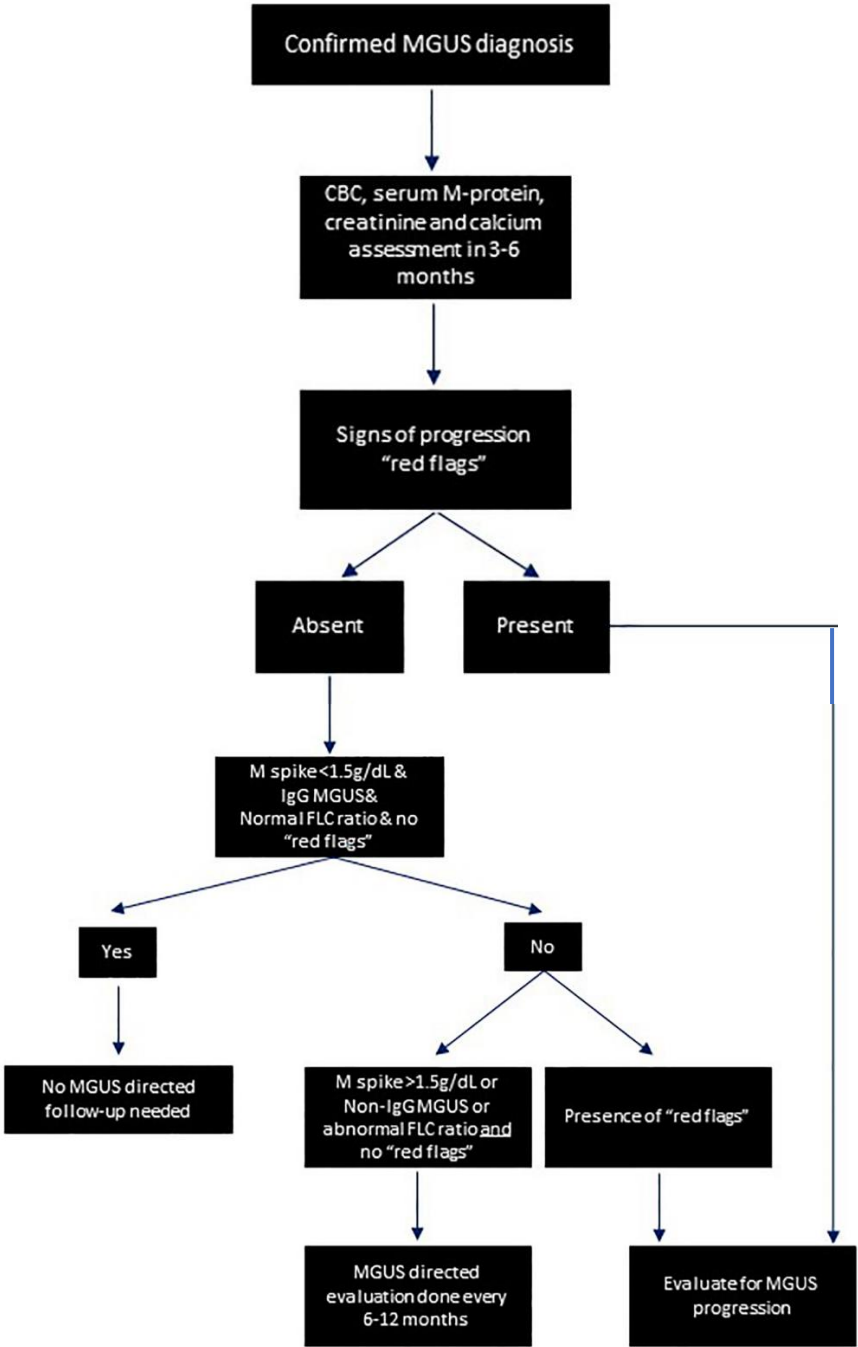
Management of MGUS
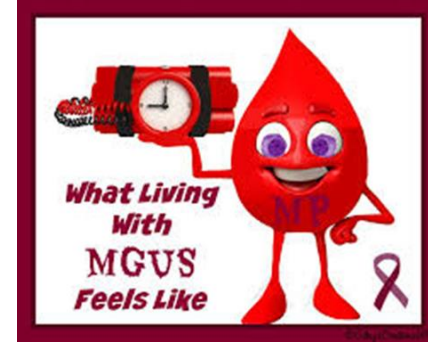
- Current management **is "watch and wait."**

- As risk of progression does not change over time, **lifelong follow-up is recommended**.

- **Low risk: SS and BM not required**, **monitor every 3 - 6 months for 2 years then 1 to 2 yearly** if stable.

- **Intermediate or high risk**: **SS and BM are mandatory**, review and monitor **as above every 3 - 6 months for 2 years then annually for life.**

- Although the risk of progression in patients with **light chain only MGUS** is relatively low (0.3% per year), there is a considerable **risk of developing renal failure**, **6-monthly follow-up is recommended.**

Maciocia et al, Hematological Oncology. 2017

Management of MGUS

- Patients with **MGUS with elevated SFLC** should be monitored for development of **amyloidosis or MGRS,** measurement of **NT-proBNP and urine albumin** at follow-up is **recommended.**

- A **BM aspirate and trephine biopsy ± skeletal survey** is always indicated if features suggestive of **end organ damage develop or if >25% increase in PP levels occurs over a 3-month period** (minimum 0.5 g/dL).

Maciocia et al, Hematological Oncology. 2017

Suggested algorithm for monitoring patients with MGUS

Jithma P. Abeykoon et al., Faculty Reviews 2022

Conclusion

MGUS is a **precursor state** for LPMs, including MM, AL and WM.

When patients with MGUS are evaluated, **accurate assessment** should be done to **risk-stratify patients** to guide **future monitoring**.

Remember: **the majority of patients with MGUS will never progress** to **an aggressive malignancy** during their lifespan, and having a diagnosis of a precancerous state could be a **psychological burden for these patients.**

With the **advent of genetic sequencing techniques** such as WES, new molecular and genetic signatures will enable better and early risk stratification of MGUS.

With future studies, we hope to be able **to better understand the pathobiology of MGUS that leads to disease progression** and to be able to **better risk-stratify patients.**

...σας ευχαριστώ πολύ για την προσοχή σας...