BIO MED J 2023

LES JOURNÉES POUR L'AVENIR DE LA BIOLOGIE MÉDICALE

9 & 10 MARS 2023 . Palais des Congrès de Paris Porte Maillot

Gammapathies Monoclonales

Place de l'analyse des immunoglobulines monoclonales

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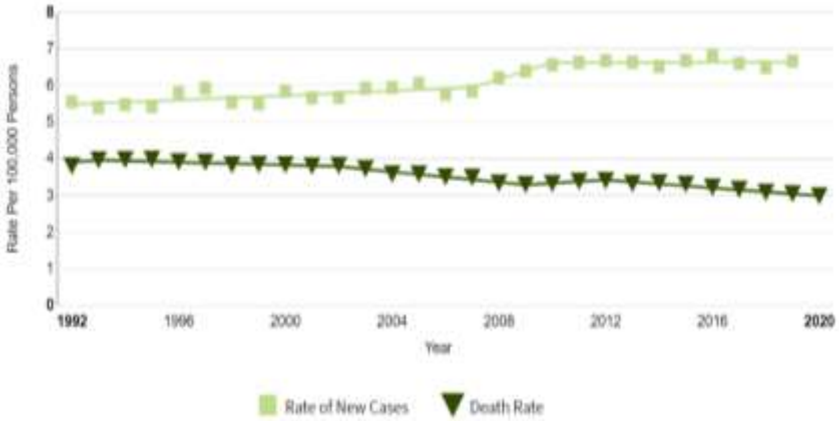
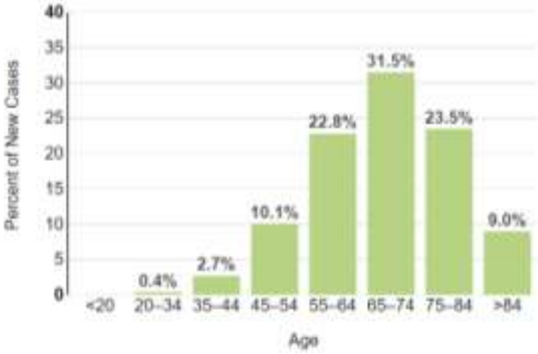
Myélome - Epidémiologie

- 1.8 % des nouveaux cas de cancers
- 2.1 % des décès par cancers
- 2^{e} hémopathie maligne

- ↑ Incidence
- ↓ Mortalité

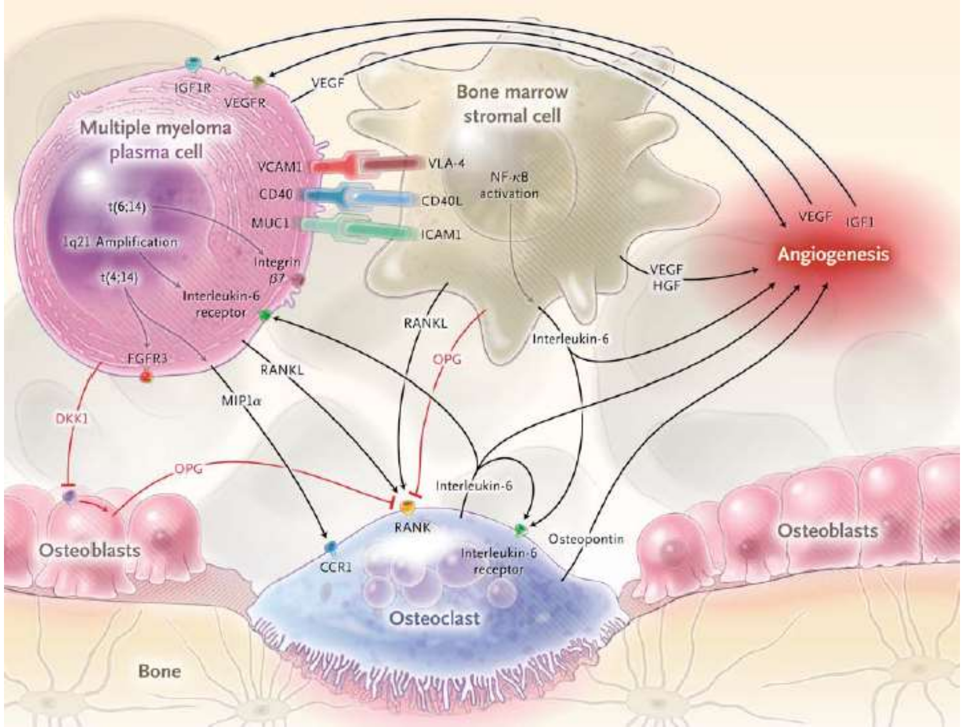
- Sex ratio H:F 1.5:1
- Age médian au diagnostic 69 ans





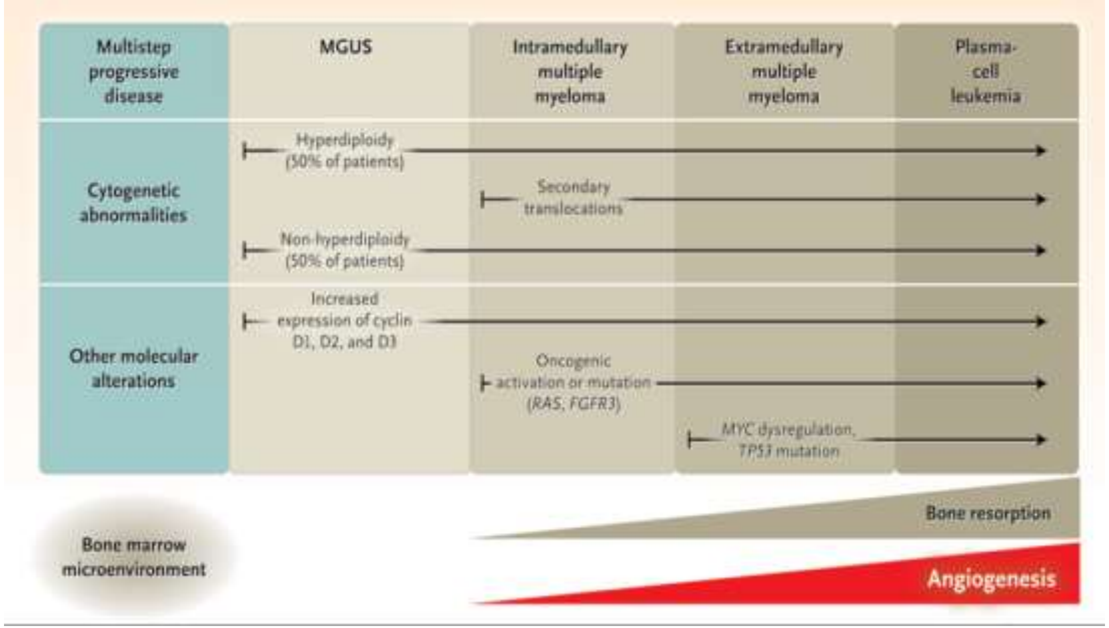
seer.cancer.gov

Myélome: Physiopathologie et signes cliniques


IGF1R
VEGFR
VEGF
Multiple myeloma plasma cell
Bone marrow stromal cell
VCAM1
VLA-4
CD40
CD40L
NF-κB activation
MUC1
ICAM1
t(6;14)
1q21 Amplification
Integrin β7
t(4;14)
Interleukin-6 receptor
VEGF
IGF1
Angiogenesis
VEGF
HGF
RANKL
OPG
Interleukin-6
FGFR3
RANKL
MIP1α
DKK1
OPG
Interleukin-6
RANK
Osteopontin
CCR1
Interleukin-6 receptor
Osteoblasts
Osteoblasts
Osteoclast
Bone

Kyle et al., NEJM, 2002

Du MGUS au Myélome: un continuum


Multistep progressive disease
MGUS
Intramedullary multiple myeloma
Extramedullary multiple myeloma
Plasma-cell leukemia
Cytogenetic abnormalities
Hyperdiploidy (50% of patients)
Secondary translocations
Non-hyperdiploidy (50% of patients)
Other molecular alterations
Increased expression of cyclin D1, D2, and D3
Oncogenic activation or mutation (RAS, FGFR3)
MYC dysregulation, TP53 mutation
Bone marrow microenvironment
Bone resorption
Angiogenesis

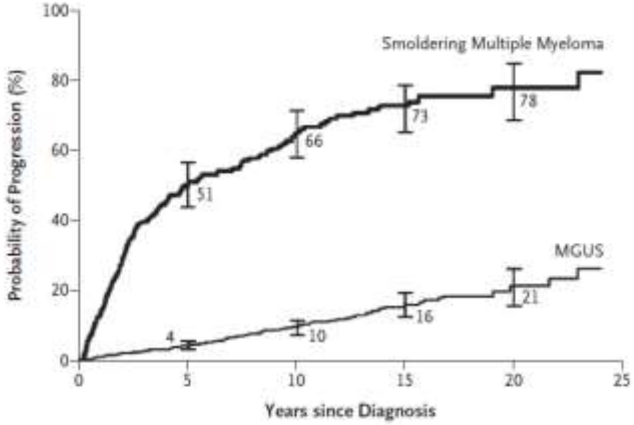


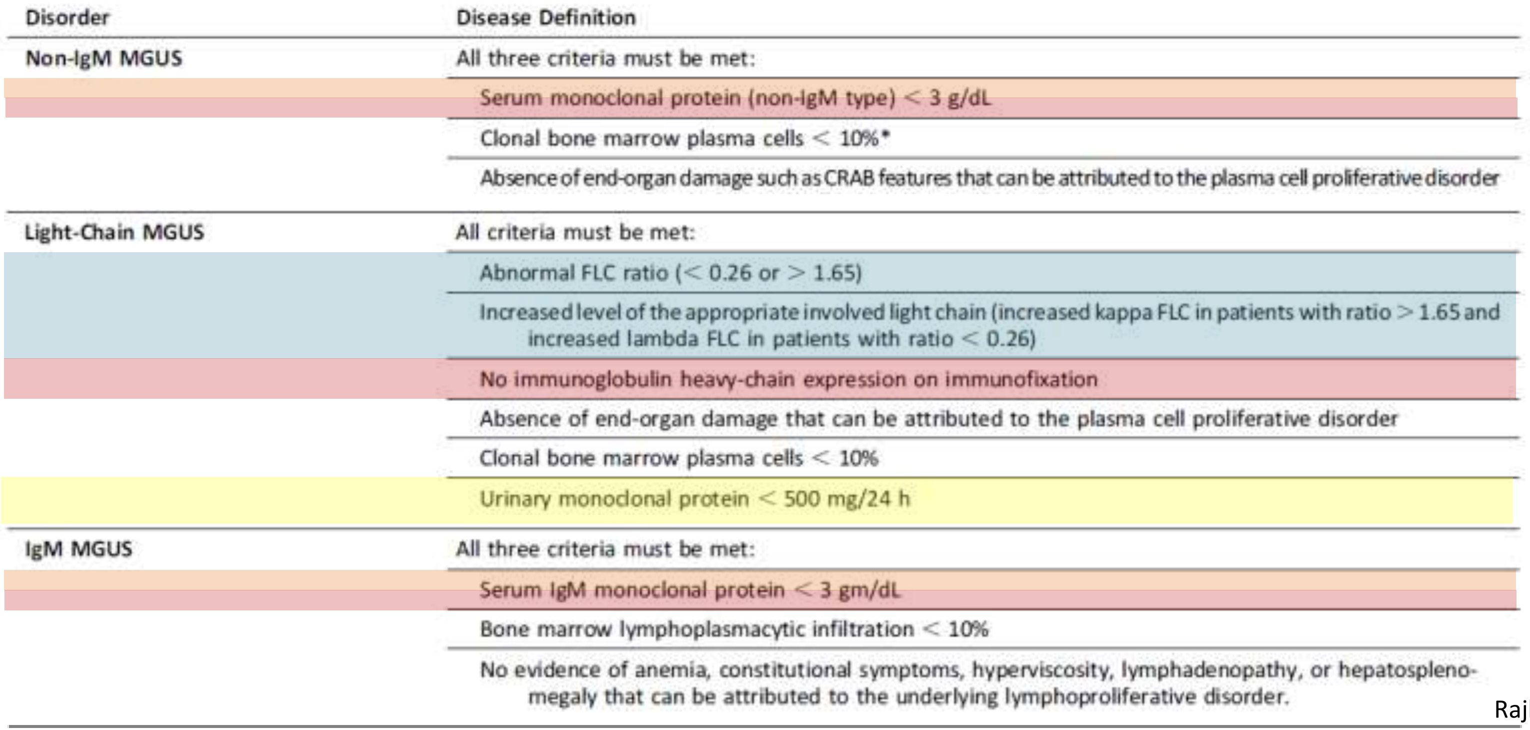
Figure 2. Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS).

I bars denote 95% confidence intervals.

Kyle et al., NEJM, 2002

Immunoglobuline monoclonale & Diagnostic du MGUS

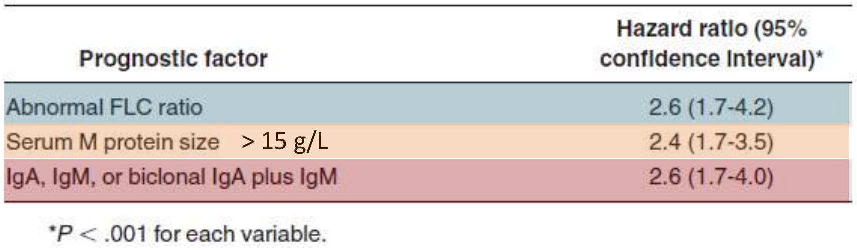
🟧 EPS
🟥 IF
🟨 EPU ou IFU
🟦 FLC



Disorder	Disease Definition
Non-IgM MGUS	All three criteria must be met:
	Serum monoclonal protein (non-IgM type) < 3 g/dL
	Clonal bone marrow plasma cells < 10%*
	Absence of end-organ damage such as CRAB features that can be attributed to the plasma cell proliferative disorder
Light-Chain MGUS	All criteria must be met:
	Abnormal FLC ratio (< 0.26 or > 1.65)
	Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with 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/24 h
IgM MGUS	All three 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.

Rajkumar et al., ASCO, 2016

Immunoglobuline monoclonale & Pronostic des MGUS



Prognostic factor	Hazard ratio (95% confidence interval)*
Abnormal FLC ratio	2.6 (1.7-4.2)
Serum M protein size > 15 g/L	2.4 (1.7-3.5)
IgA, IgM, or biclonal IgA plus IgM	2.6 (1.7-4.0)

*$P < .001$ for each variable.

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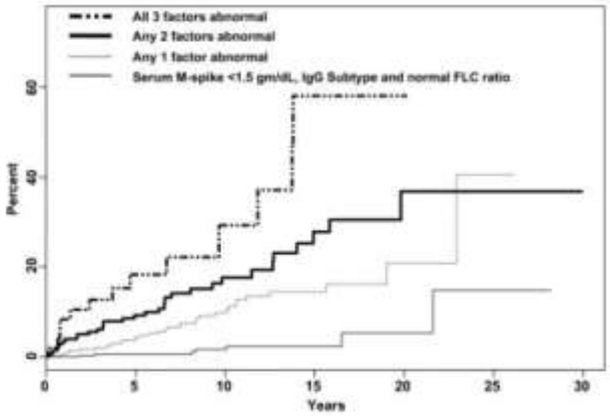
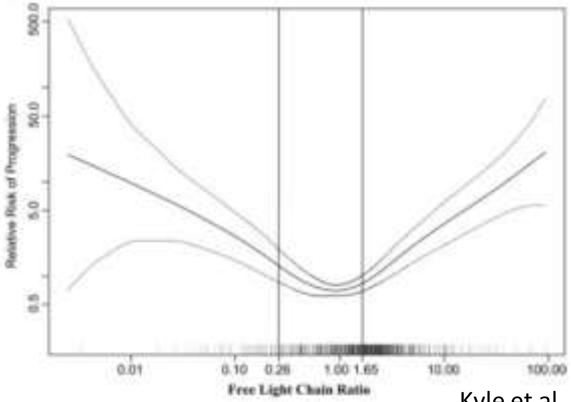
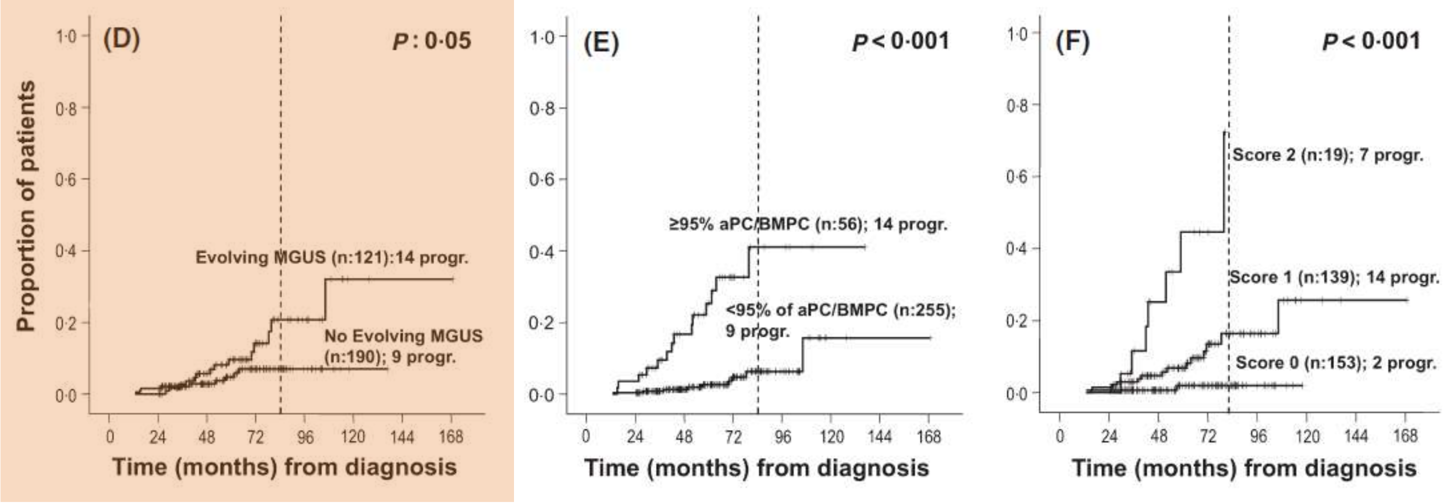




Kyle et al., NEJM, 2007

Immunoglobuline monoclonale & Suivi des MGUS



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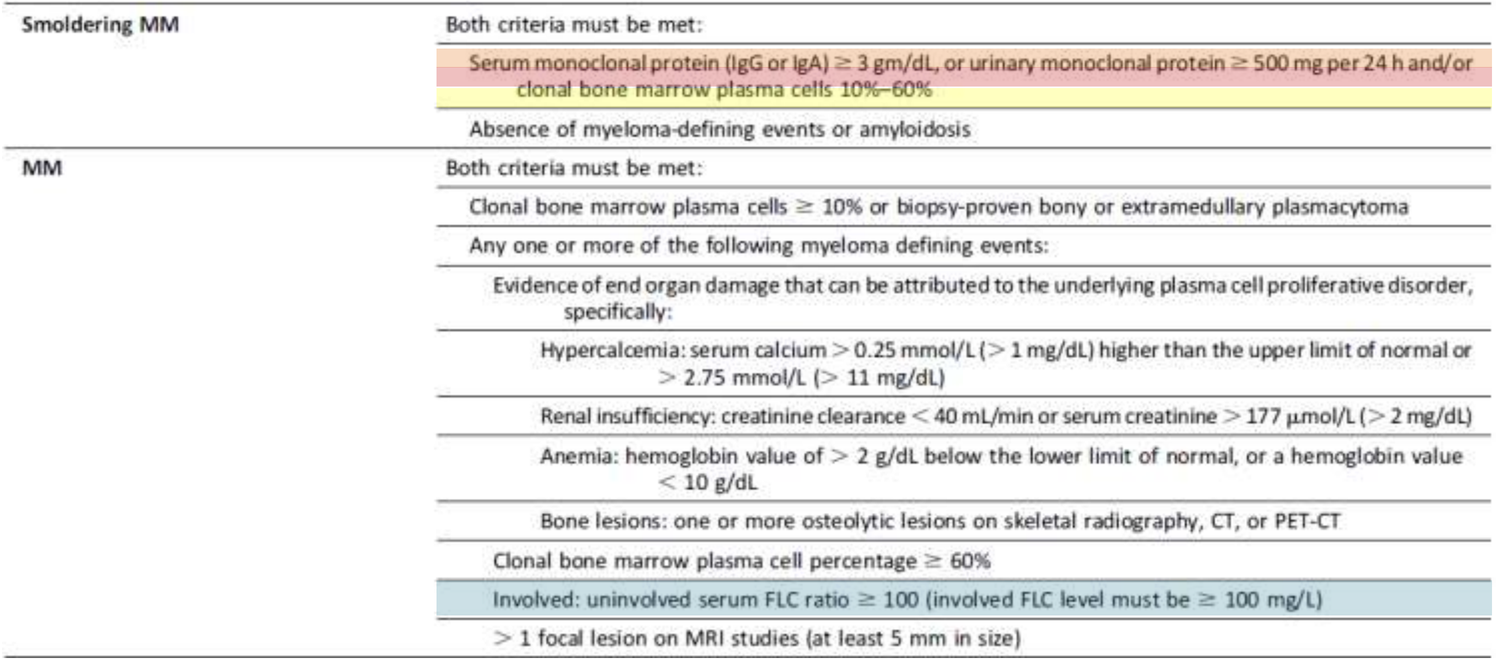
*Evolving MGUS is defined as an increase of M-protein of at least 10% by the third year, confirmed by two consecutive measurements separated by at least 1 month.

Perez-Persona et al., Br J Hematol, 2009

Immunoglobuline monoclonale & Diagnostic des SMM & MM

🟧 EPS
🟥 IF
🟨 EPU ou IFU
🟦 FLC



Smoldering MM	Both criteria must be met:
	Serum monoclonal protein (IgG or IgA) ≥ 3 gm/dL, or urinary monoclonal protein ≥ 500 mg per 24 h and/or clonal bone marrow plasma cells 10%–60%
	Absence of myeloma-defining events or amyloidosis
MM	Both criteria must be met:
	Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma
	Any one or more of the following myeloma defining events:
	Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
	Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL)
	Renal insufficiency: creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L (> 2 mg/dL)
	Anemia: hemoglobin value of > 2 g/dL below the lower limit of normal, or a hemoglobin value < 10 g/dL
	Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
	Clonal bone marrow plasma cell percentage ≥ 60%
	Involved: uninvolved serum FLC ratio ≥ 100 (involved FLC level must be ≥ 100 mg/L)
	> 1 focal lesion on MRI studies (at least 5 mm in size)

Rajkumar et al., ASCO, 2016

Immunoglobuline monoclonale & Pronostic du SMM

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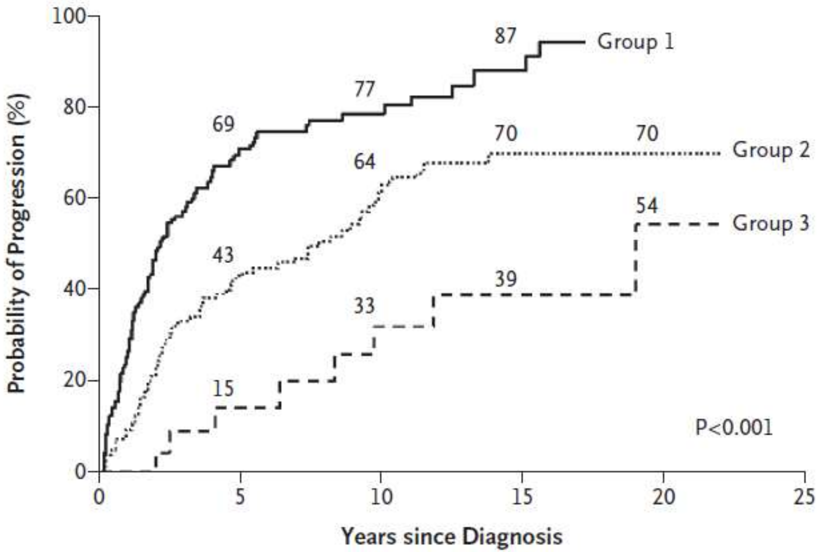

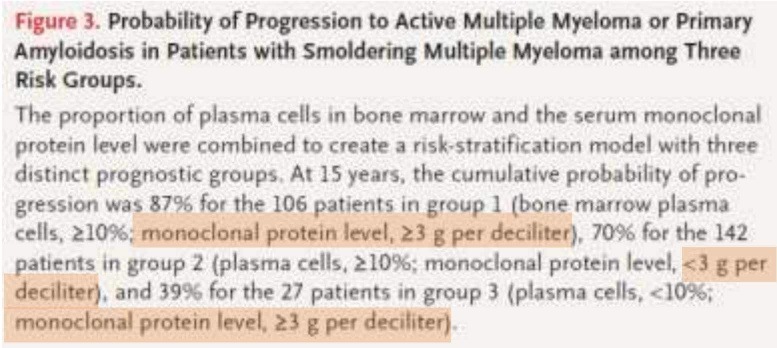
Figure 3. Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma among Three Risk Groups.

The proportion of plasma cells in bone marrow and the serum monoclonal protein level were combined to create a risk-stratification model with three distinct prognostic groups. At 15 years, the cumulative probability of progression was 87% for the 106 patients in group 1 (bone marrow plasma cells, ≥10%; monoclonal protein level, ≥3 g per deciliter), 70% for the 142 patients in group 2 (plasma cells, ≥10%; monoclonal protein level, <3 g per deciliter), and 39% for the 27 patients in group 3 (plasma cells, <10%; monoclonal protein level, ≥3 g per deciliter).

Kyle et al., NEJM, 2007

Immunoglobuline monoclonale & Pronostic du SMM

🟧 EPS
🟥 IF
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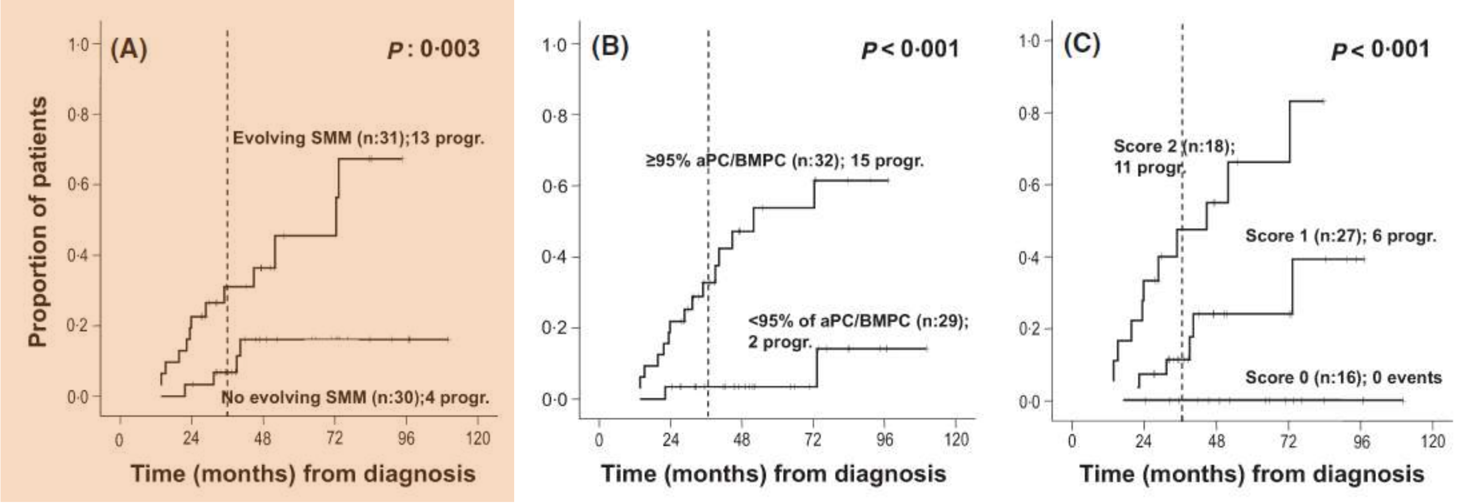
🟦 FLC



*Evolving MGUS is defined as an increase of M-protein of at least 10% by the third year, confirmed by two consecutive measurements separated by at least 1 month.

Perez-Persona et al., Br J Hematol, 2009

Immunoglobuline monoclonale & Pronostic du MM

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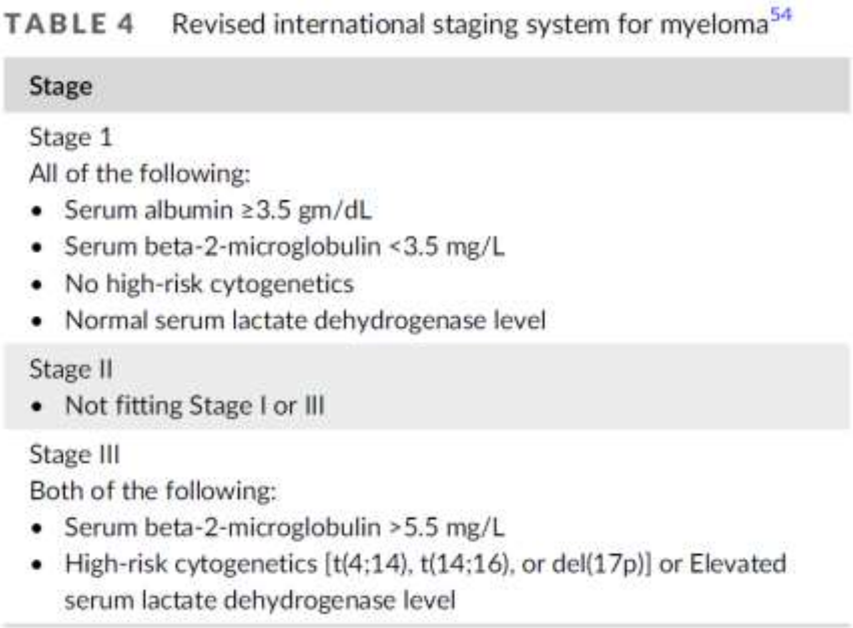


TABLE 4 Revised international staging system for myeloma[54]

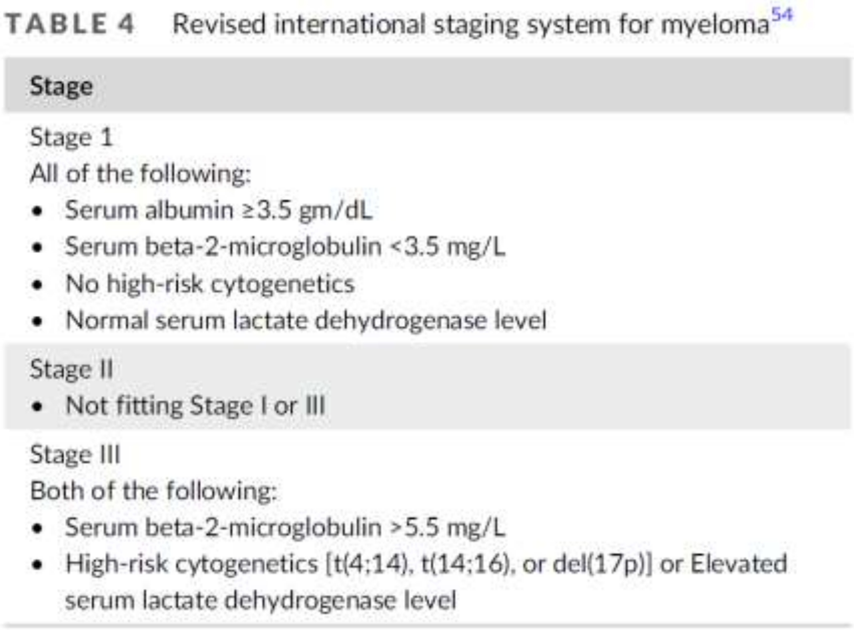
Stage
Stage 1 All of the following: • Serum albumin ≥3.5 gm/dL • Serum beta-2-microglobulin <3.5 mg/L • No high-risk cytogenetics • Normal serum lactate dehydrogenase level
Stage II • Not fitting Stage I or III
Stage III Both of the following: • Serum beta-2-microglobulin >5.5 mg/L • High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or Elevated serum lactate dehydrogenase level

?

Rajkumar et al., AJH, 2022

Immunoglobuline monoclonale & Pronostic du MM

🟧 EPS
🟥 IF
🟨 EPU ou IFU
🟦 FLC



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?

IgA MM	↑ ISS-3 ↑ anemie ↑ t(4;14)
FLC MM	↑ IR ↑ t(11;14)

Bal et al., Ann Hematol., 2022

Immunoglobuline monoclonale & Réponse au traitement

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🟨 EPU ou IFU
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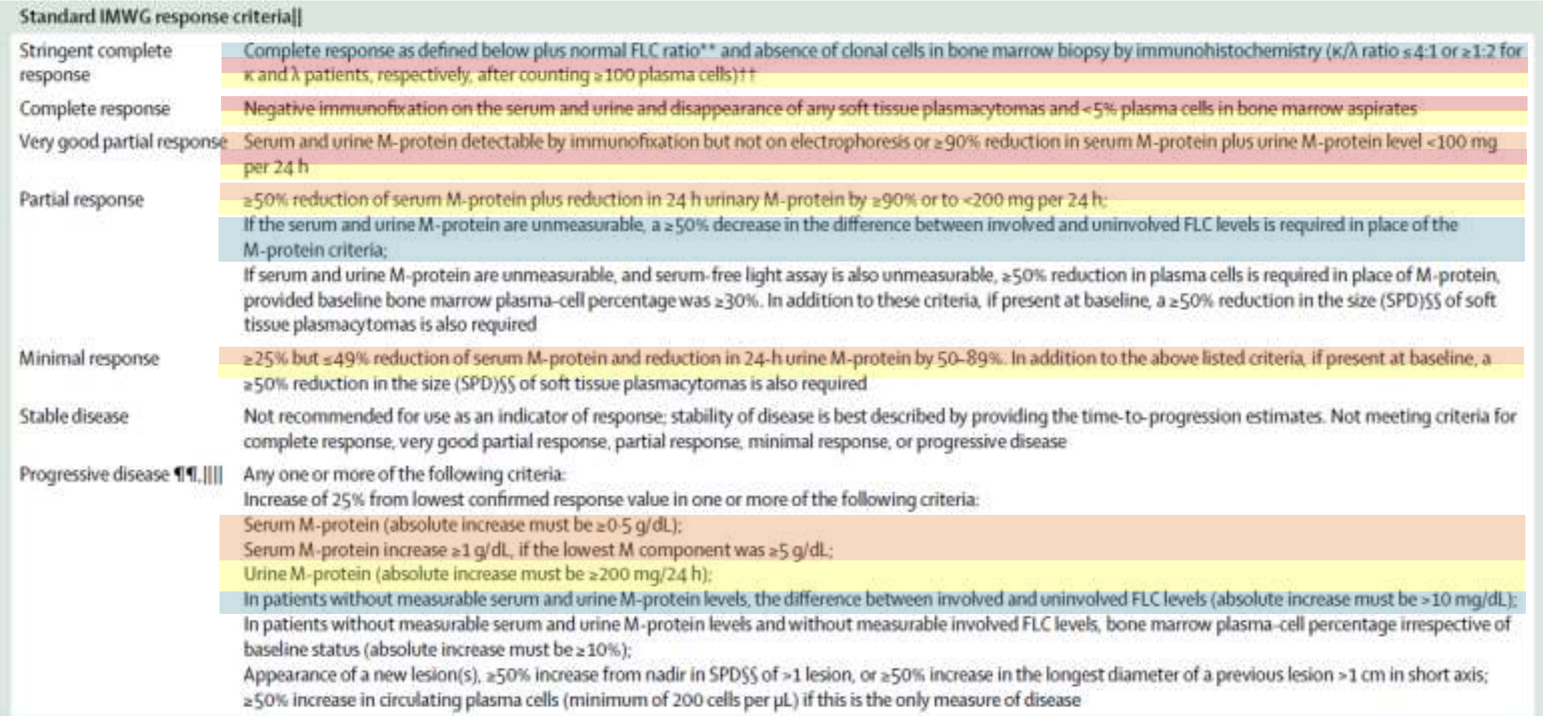


Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Kumar et al., Lancet Oncol., 2016

Quelle place pour l’électrophorèse et l’immunofixation des urines ?

- Ne fait pas partie des critères diagnostiques du MM
- **Mais** fait partie des critères pour différencier FLC SMM Vs FLC MGUS
- **Ou** si suspicion d’amylose AL

- Préférentiellement sur des urines de 24h
- Préférentiellement sur des urines concentrées (Levinson, 2011)

- Exclusion d’une gammapathie dans le diagnostic d’une pathologie rénale
- Evaluation de l’atteinte rénale dans le bilan d’une gammapathie

Levinson., 2011

Hors du continuum: les Gammapathies Monoclonales de Signification Clinique

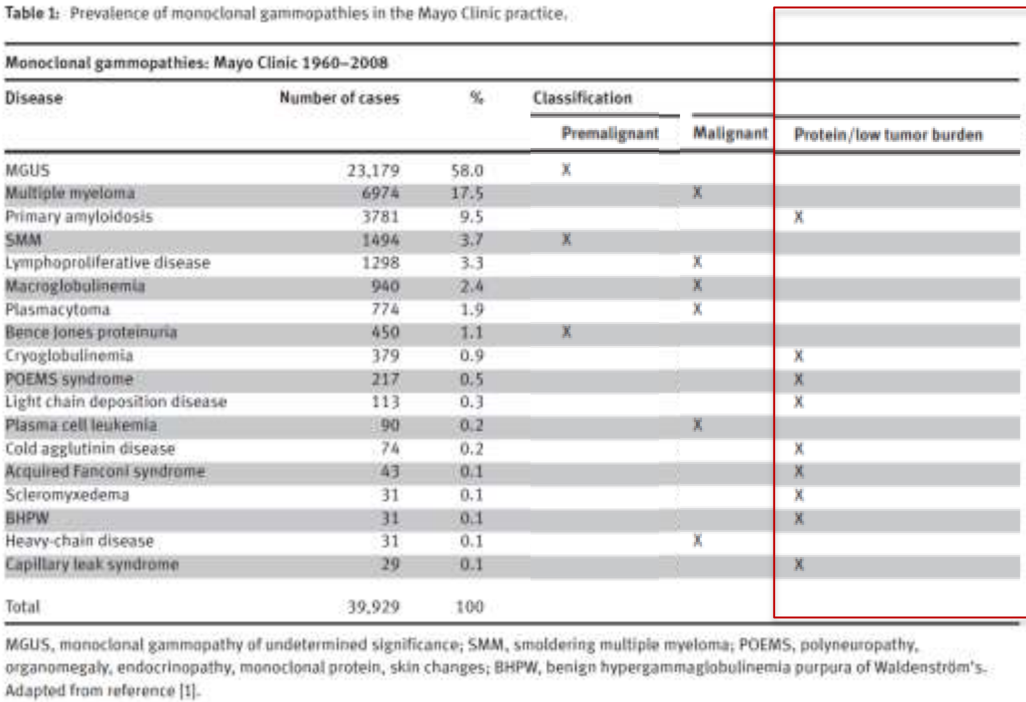


Table 1: Prevalence of monoclonal gammopathies in the Mayo Clinic practice.

Monoclonal gammopathies: Mayo Clinic 1960–2008

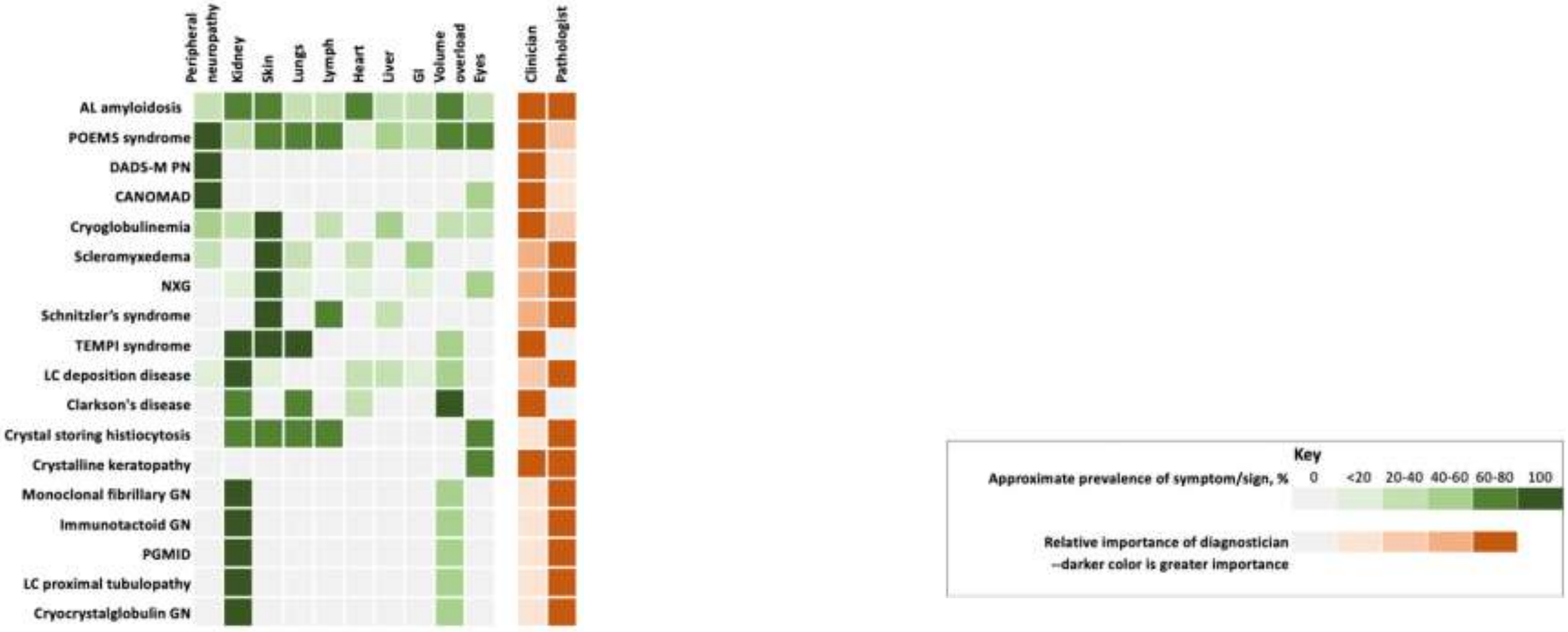
Disease	Number of cases	%	Classification		
			Premalignant	Malignant	Protein/low tumor burden
MGUS	23,179	58.0	X		
Multiple myeloma	6974	17.5		X	
Primary amyloidosis	3781	9.5			X
SMM	1494	3.7	X		
Lymphoproliferative disease	1298	3.3		X	
Macroglobulinemia	940	2.4		X	
Plasmacytoma	774	1.9		X	
Bence Jones proteinuria	450	1.1	X		
Cryoglobulinemia	379	0.9			X
POEMS syndrome	217	0.5			X
Light chain deposition disease	113	0.3			X
Plasma cell leukemia	90	0.2		X	
Cold agglutinin disease	74	0.2			X
Acquired Fanconi syndrome	43	0.1			X
Scleromyxedema	31	0.1			X
BHPW	31	0.1			X
Heavy-chain disease	31	0.1		X	
Capillary leak syndrome	29	0.1			X
Total	39,929	100			

MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; BHPW, benign hypergammaglobulinemia purpura of Waldenström's. Adapted from reference [1].

MGCS
due à une Igmo
pathogène

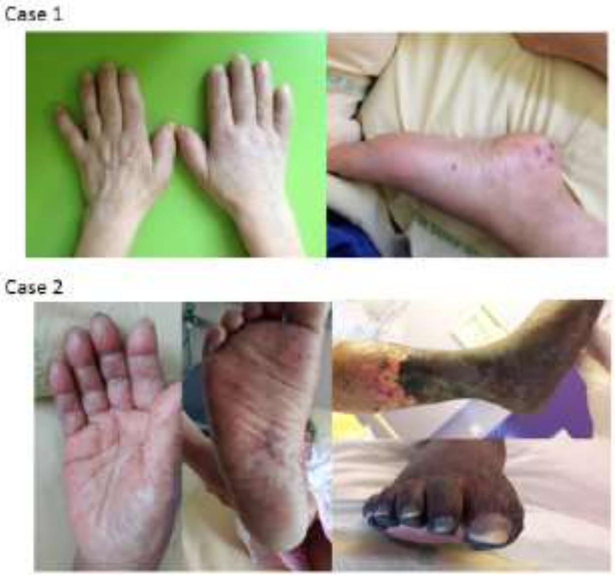
Levinson., 2011

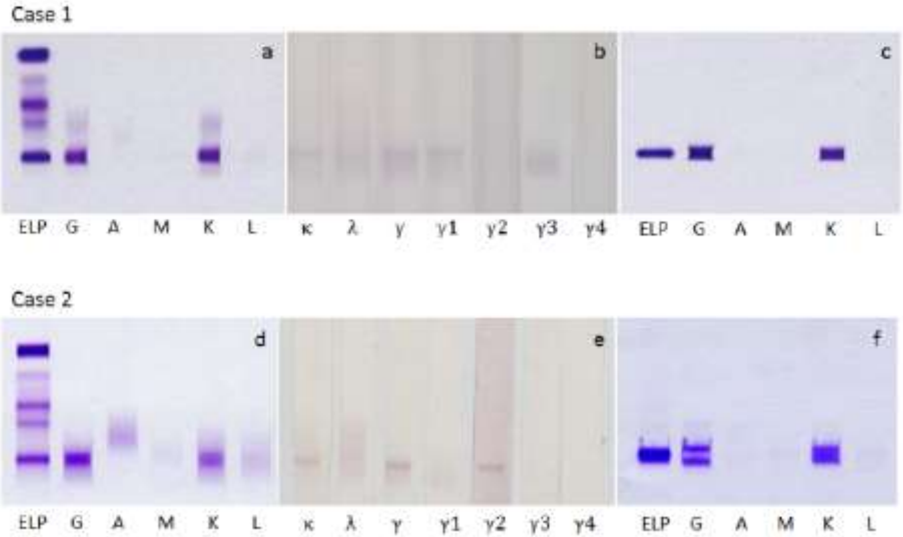
Atteintes d’organes et diagnostic des MGCS



Dispenzieri et al., Hematology, 2020

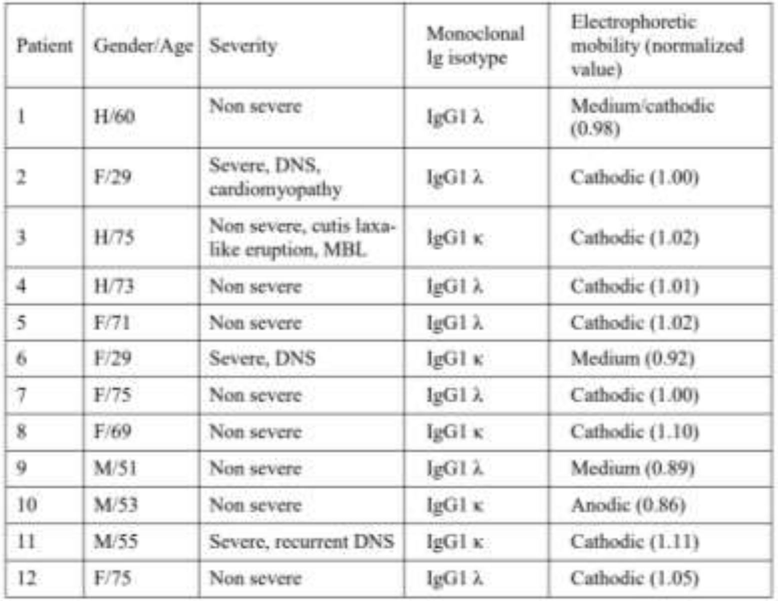
Particularités immunochimiques des MGCS : l’exemple des cryoglubulinémies


Case 1
Case 2

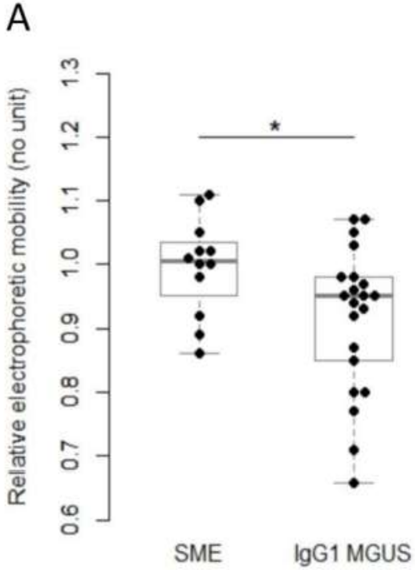

Case 1
a
b
c
ELP G A M K L
κ λ γ γ1 γ2 γ3 γ4
ELP G A M K L
Case 2
d
e
f
ELP G A M K L
κ λ γ γ1 γ2 γ3 γ4
ELP G A M K L

Petersen et al., Clin Lab., 2018

Particularités immunochimiques des MGCS : l'exemple du scléromyxoedème

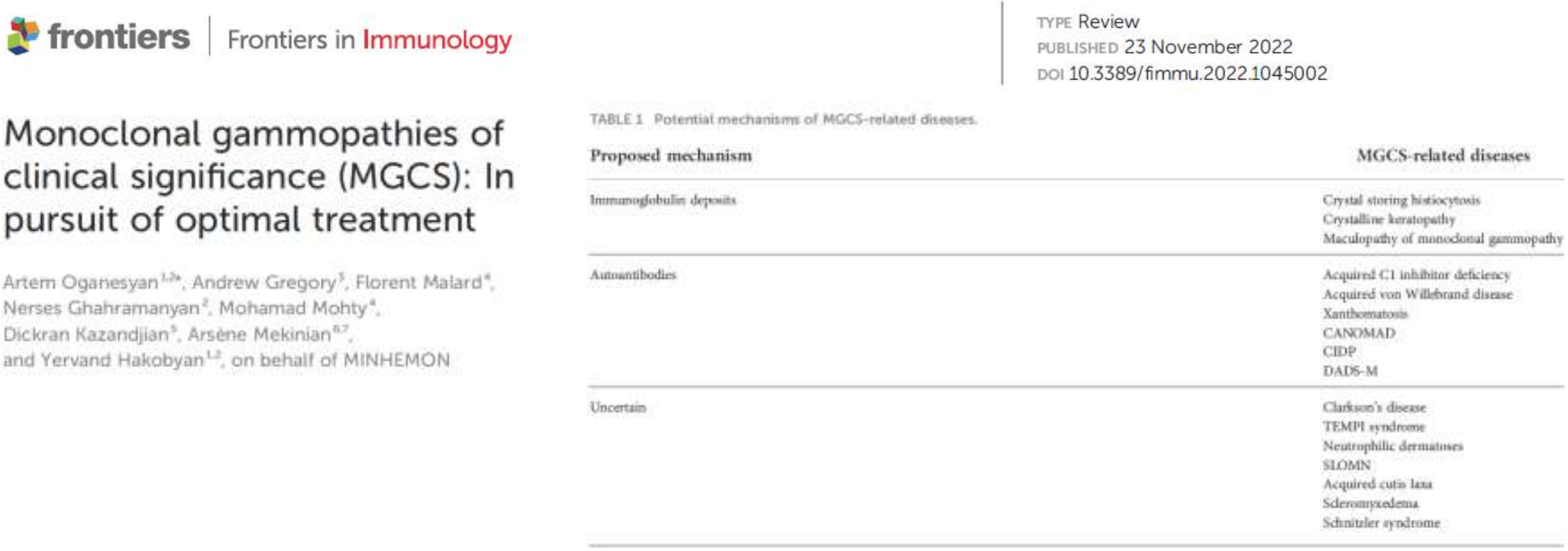


Patient	Gender/Age	Severity	Monoclonal Ig isotype	Electrophoretic mobility (normalized value)
1	H/60	Non severe	IgG1 λ	Medium/cathodic (0.98)
2	F/29	Severe, DNS, cardiomyopathy	IgG1 λ	Cathodic (1.00)
3	H/75	Non severe, cutis laxa-like eruption, MBL	IgG1 κ	Cathodic (1.02)
4	H/73	Non severe	IgG1 λ	Cathodic (1.01)
5	F/71	Non severe	IgG1 λ	Cathodic (1.02)
6	F/29	Severe, DNS	IgG1 κ	Medium (0.92)
7	F/75	Non severe	IgG1 λ	Cathodic (1.00)
8	F/69	Non severe	IgG1 κ	Cathodic (1.10)
9	M/51	Non severe	IgG1 λ	Medium (0.89)
10	M/53	Non severe	IgG1 κ	Anodic (0.86)
11	M/55	Severe, recurrent DNS	IgG1 κ	Cathodic (1.11)
12	F/75	Non severe	IgG1 λ	Cathodic (1.05)



Petersen et al., Clin Lab., 2021

Physiopathologie & Implications pour la prise en charge des MGCS



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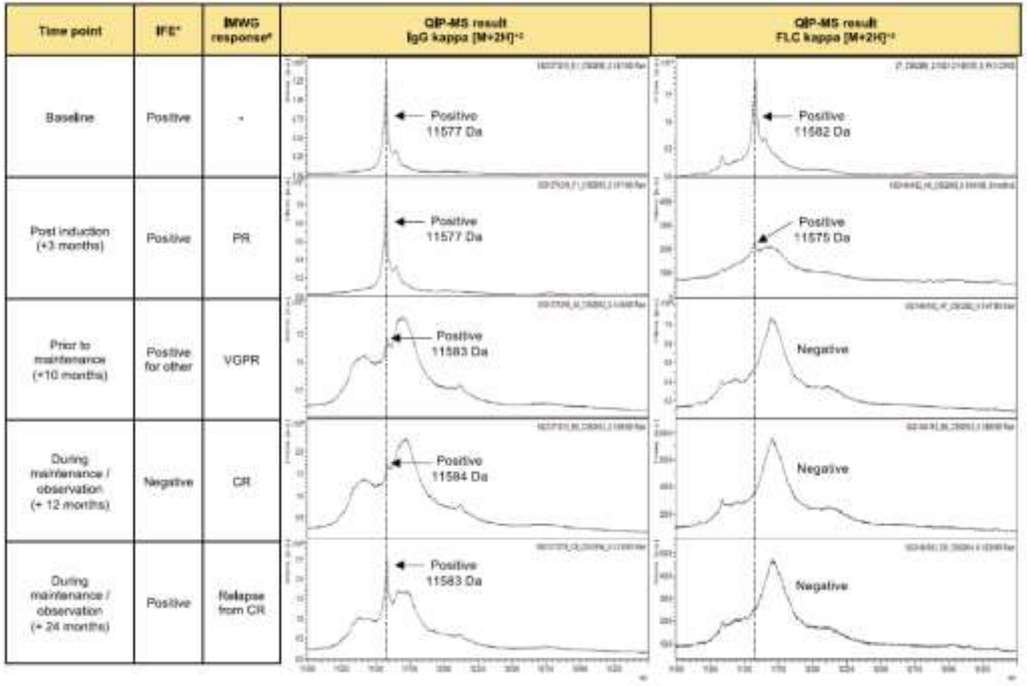
Monoclonal gammopathies of clinical significance (MGCS): In pursuit of optimal treatment

Artem Oganesyan[1,2*], Andrew Gregory[3], Florent Malard[4],
Nerses Ghahramanyan[2], Mohamad Mohty[4],
Dickran Kazandjian[5], Arsène Mekinian[6,7],
and Yervand Hakobyan[1,2], on behalf of MINHEMON

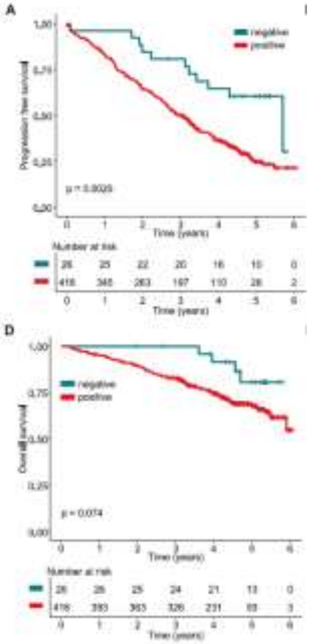
TABLE 1 Potential mechanisms of MGCS-related diseases.

Proposed mechanism	MGCS-related diseases
Immunoglobulin deposits	Crystal storing histiocytosis Crystalline keratopathy Maculopathy of monoclonal gammopathy
Autoantibodies	Acquired C1 inhibitor deficiency Acquired von Willebrand disease Xanthomatosis CANOMAD CIDP DADS-M
Uncertain	Clarkson's disease TEMPI syndrome Neutrophilic dermatoses SLOMN Acquired cutis laxa Scleromyxedema Schnitzler syndrome

Ouverture : Analyse des gammapathies par Spectrométrie de Masse



Time point	IFE*	IMWG response*	QIP-MS result IgG kappa [M+2H]+2	QIP-MS result FLC kappa [M+2H]+2
Baseline	Positive	-	Positive 11577 Da	Positive 11582 Da
Post induction (+3 months)	Positive	PR	Positive 11577 Da	Positive 11575 Da
Prior to maintenance (+10 months)	Positive for other	VGPR	Positive 11583 Da	Negative
During maintenance / observation (+ 12 months)	Negative	CR	Positive 11584 Da	Negative
During maintenance / observation (+ 24 months)	Positive	Relapse from CR	Positive 11583 Da	Negative



Mai et al., Blood Cancer Journal., 2023

MYELOME MULTIPLE

Merci de votre attention !