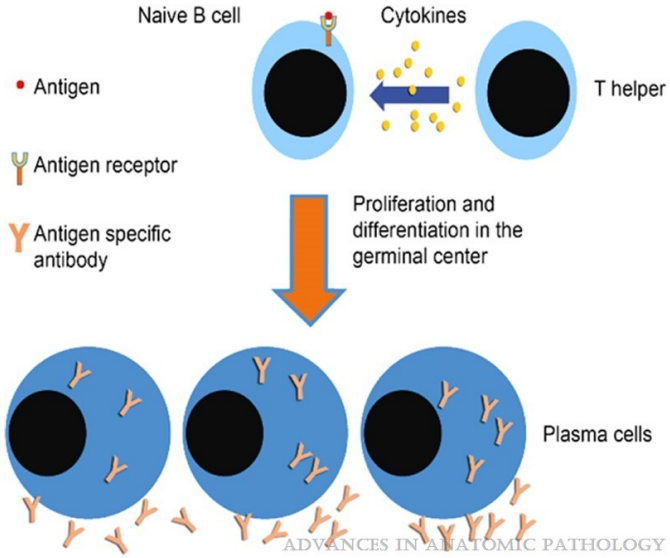
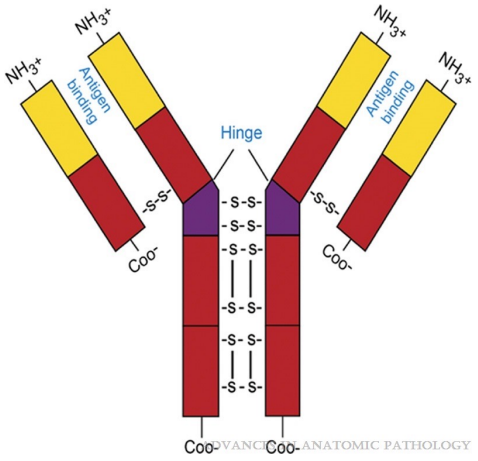
LA GAMMAPATIA MONOCLONALE DI SIGNIFICATO RENALE (MGRS): UNA ENTITÀ CLINICA POCO CONOSCIUTA

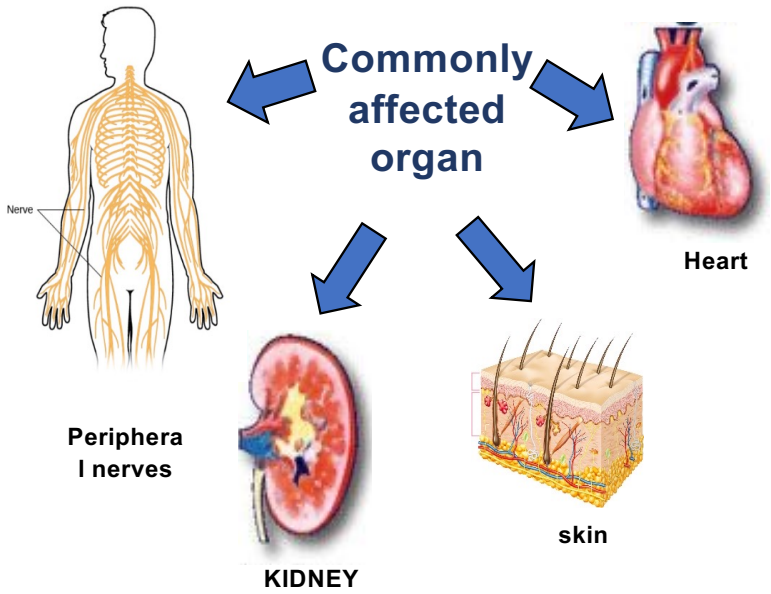
ANTONIA CAGNETTA, MD

Monoclonal Gammopathies

MG RFLECT A WIDE SPECTRUM OF RELATED-DISEASES IN WHICH INCREASED AMOUNTS OF IMMUNOGLOBULINS, PRODUCED BY A CLONE OF PLASMA-CELLS OR B LYMPHOCYTES, INDUCE END-ORGAN DAMAGE AS A RESULT OF THEIR INTRINSIC PHYSICOCHEMICAL PROPERTIES.



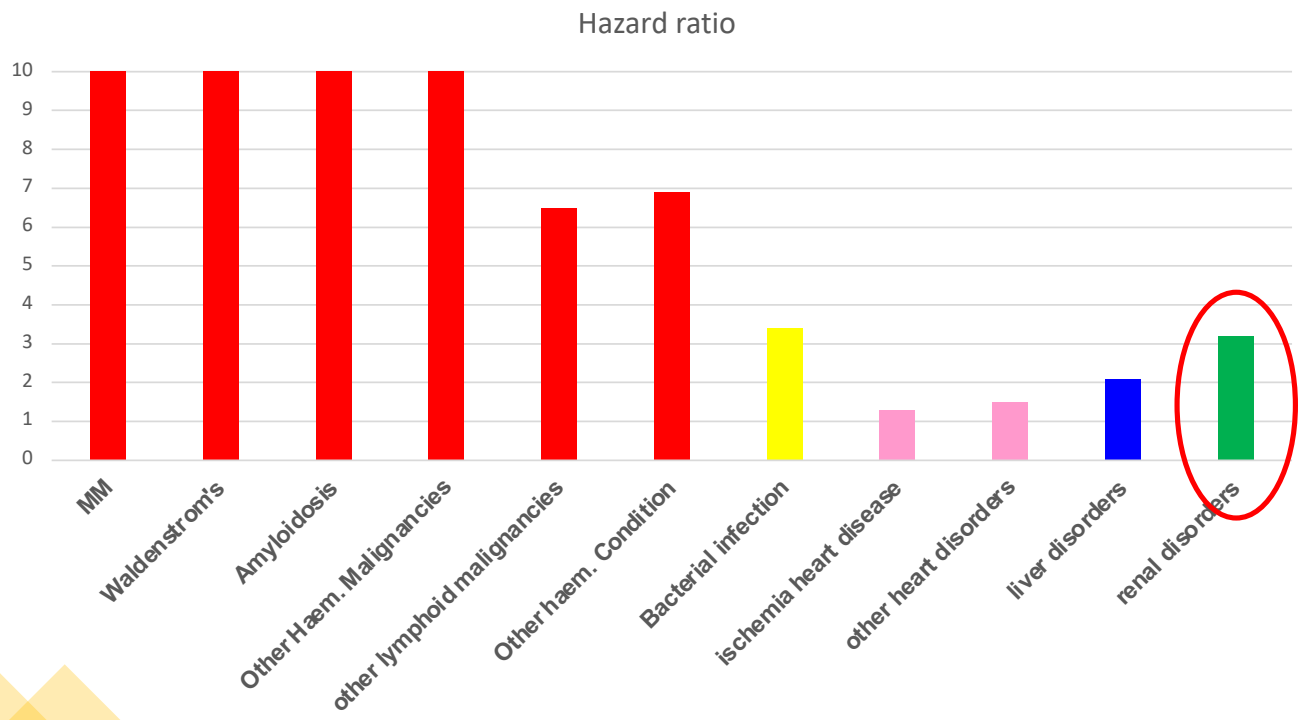




Al-Hussain T. et al. Adv Anat Pathol 2015: 22(2):121-134
Jain A. et al. Blood Adv 2019: 3 (15): 2409-2423

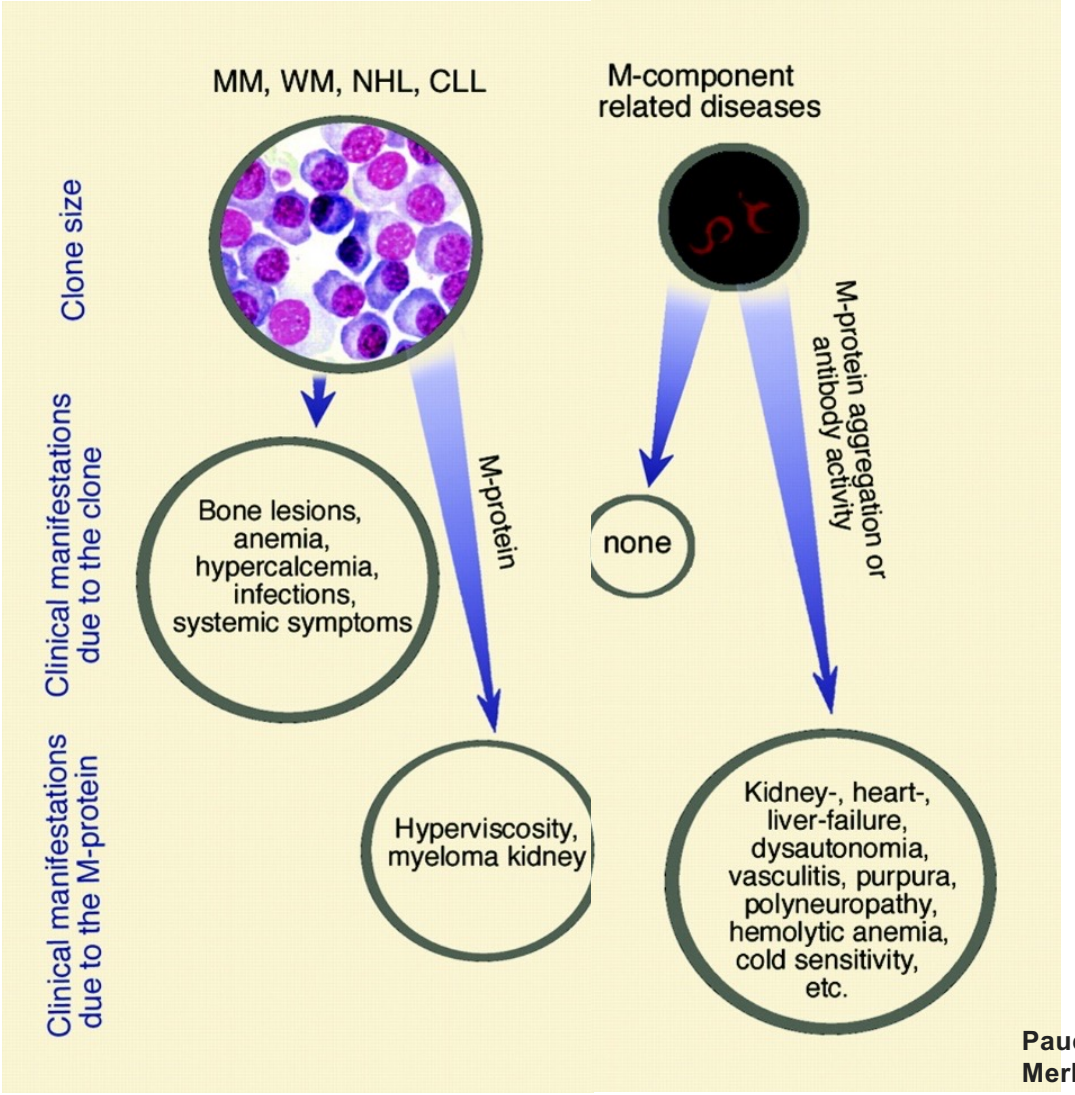
Monoclonal Gammopathies

MGUS PATIENTS HAVE INCREASED RISK OF DYING FROM A NUMBER OF CONDITIONS- INCLUDING RENAL DISEASES



Adapted from Kristinsson S. et al. Haematologica 2009;94, 1714-20

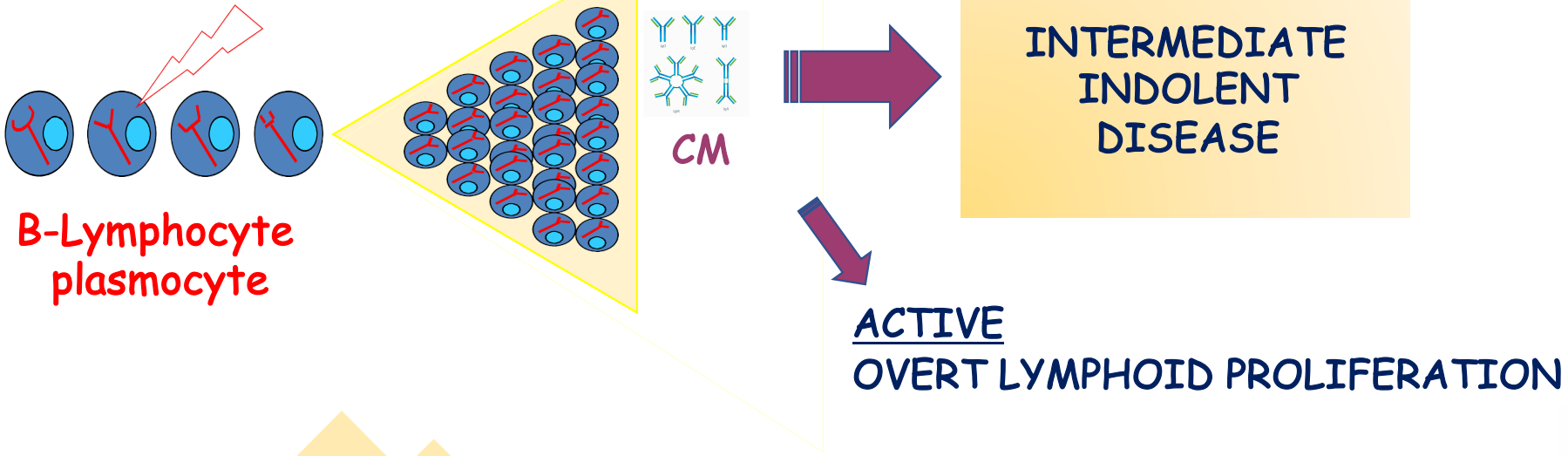
MGUS: NOT AN "INNOCENT" MONOCLONAL GAMMOPATHY



Dangerous
small B-cell clones

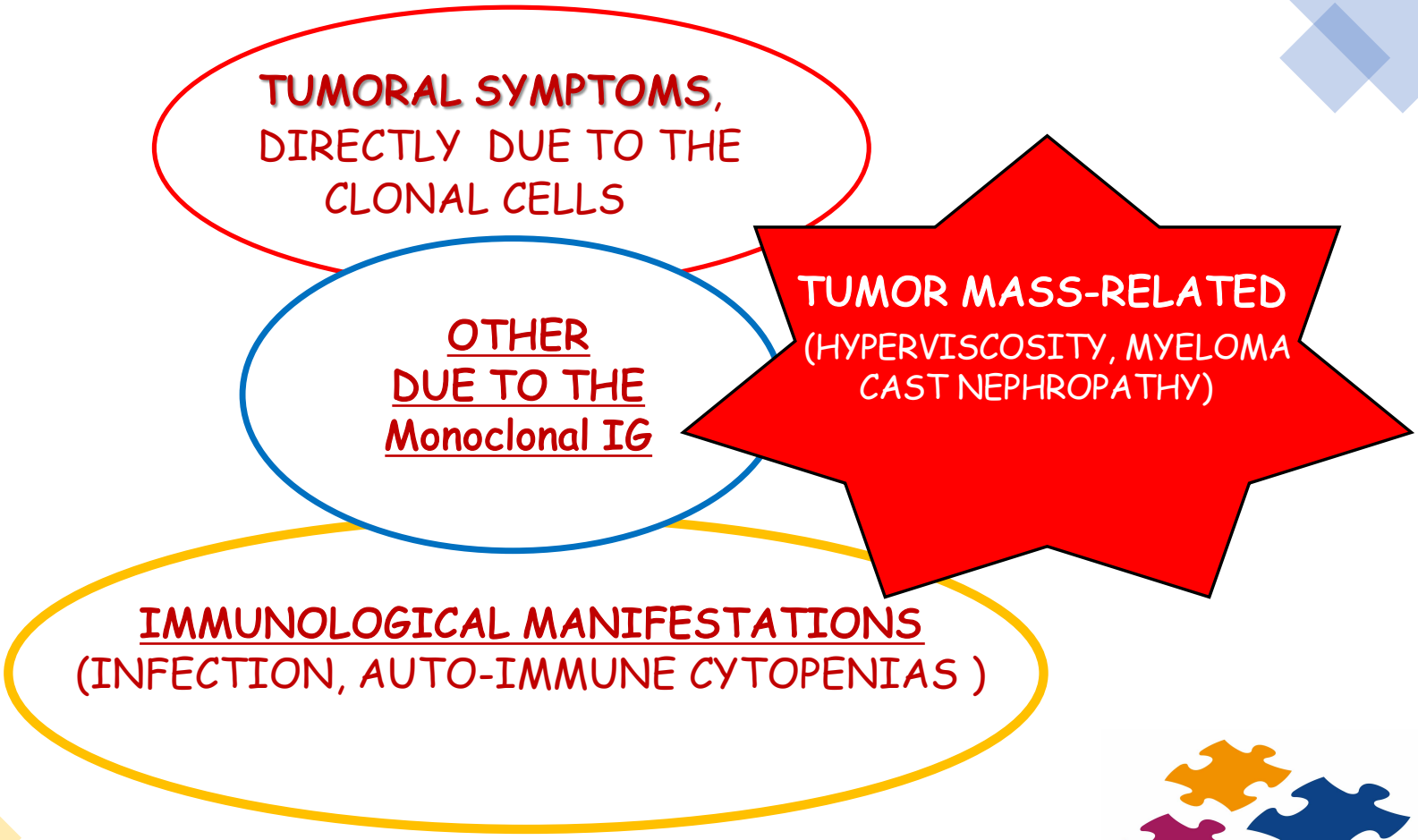
Paueksakon, P., et al. *Am. J. Kidney Dis.* 42, 87–95 (2003)
Merlini G. et al. Blood 2006;108 (8)

BIOLOGY OF MGUS

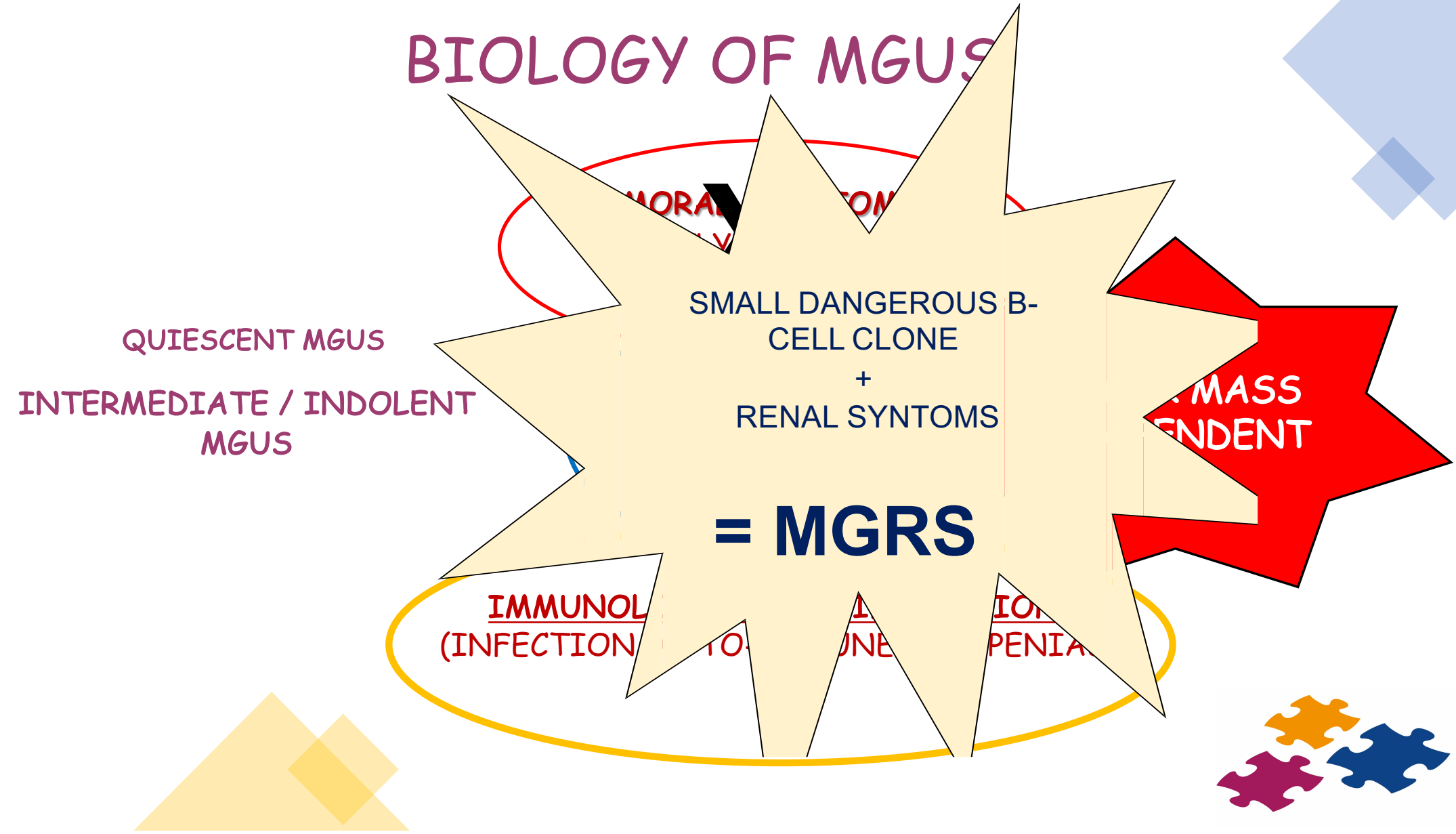


BIOLOGY OF MGUS

ACTIVE
OVERT LYMPHOID PROLIFERATION



BIOLOGY OF MGUS



Monoclonal Gammopathy of Renal Significance

TERM COINED IN 2012 (IKMG) TO ENABLE TREATMENT OF A SUBSET OF MONOCLONAL GAMMOPATHY PATIENTS WITH RENAL DYSFUNCTION

- MGRS indicates SMALL B/PLASMA CELL CLONE IN THE BM (≤10%) PRODUCING MONOCLONAL PROTEIN WHICH IS "MALIGNANT" FOR THE KIDNEYS
- ORGAN DAMAGE IS CAUSED BY M-PROTEIN/FREE LIGHT CHAINS VIA DIRECT OR INDIRECT MECHANISM
- KIDNEY BIOPSY IS ESSENTIAL TO CHARACTERIZE RENAL DAMAGE

BENIGN CONDITION WITH MALIGNANT POTENTIAL

PATHOGENESIS OF MGRS

Mechanism of Pathogenicity of Monoclonal IG

DIRECT

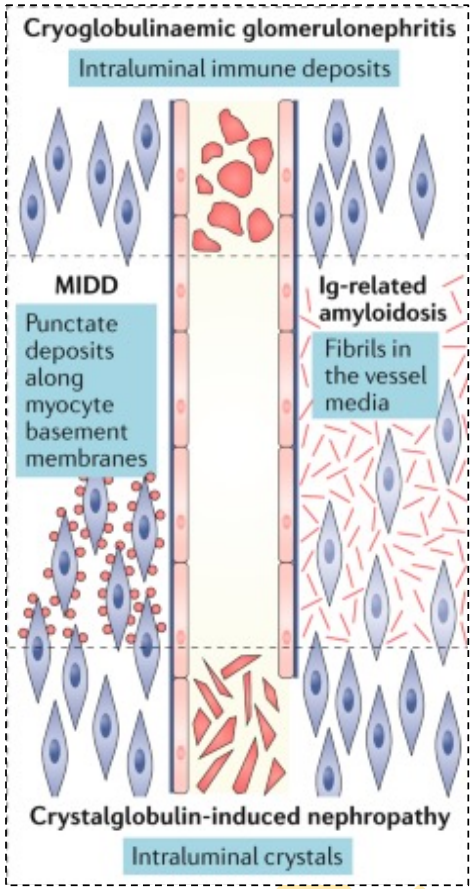
- Deposition
- Precipitation

INDIRECT

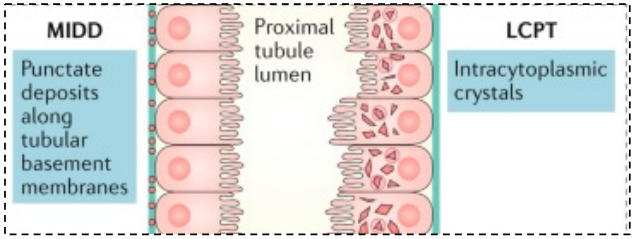
- Inflammation
- Antibody mediated injury
- Complement activation

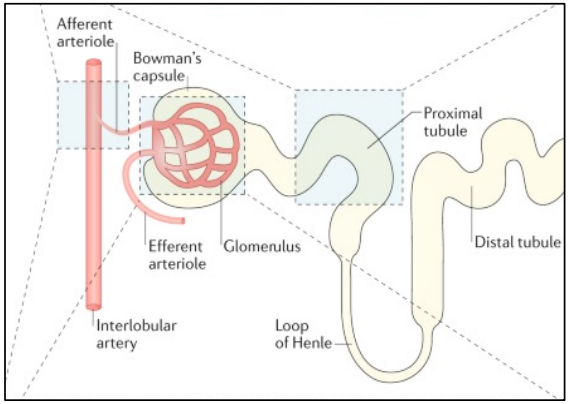
Jain A. et al. Blood Adv. 2019: 3 (15): 2409-2423
Bridoux f. Kidney Int. 2015; 87(4):698-711

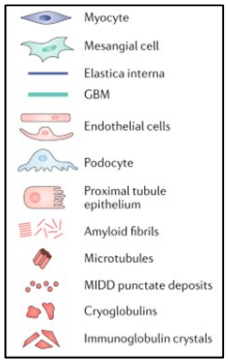
AFFERENT ARTERIOLE



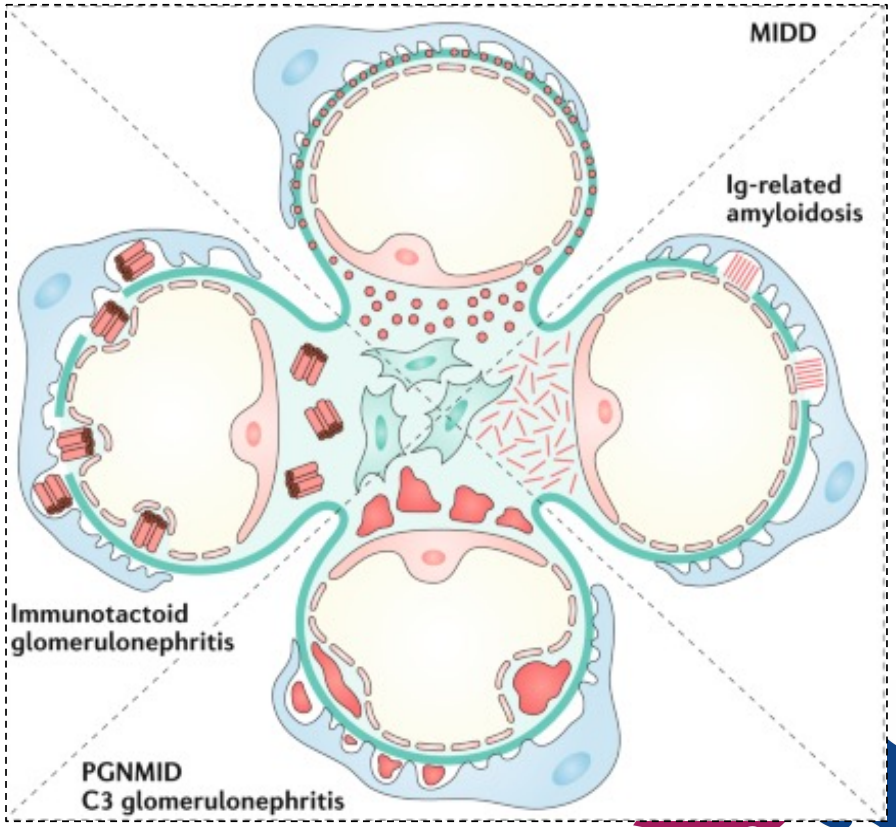
PROXIMAL TUBULE



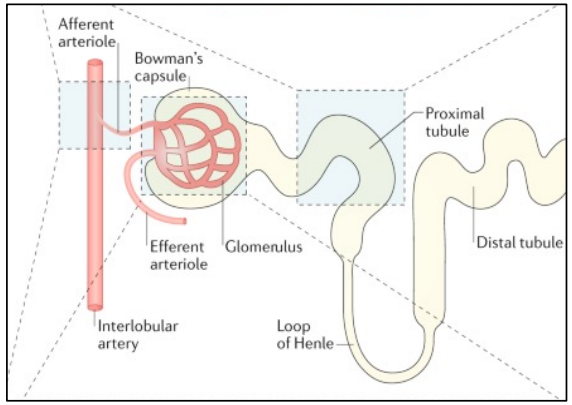


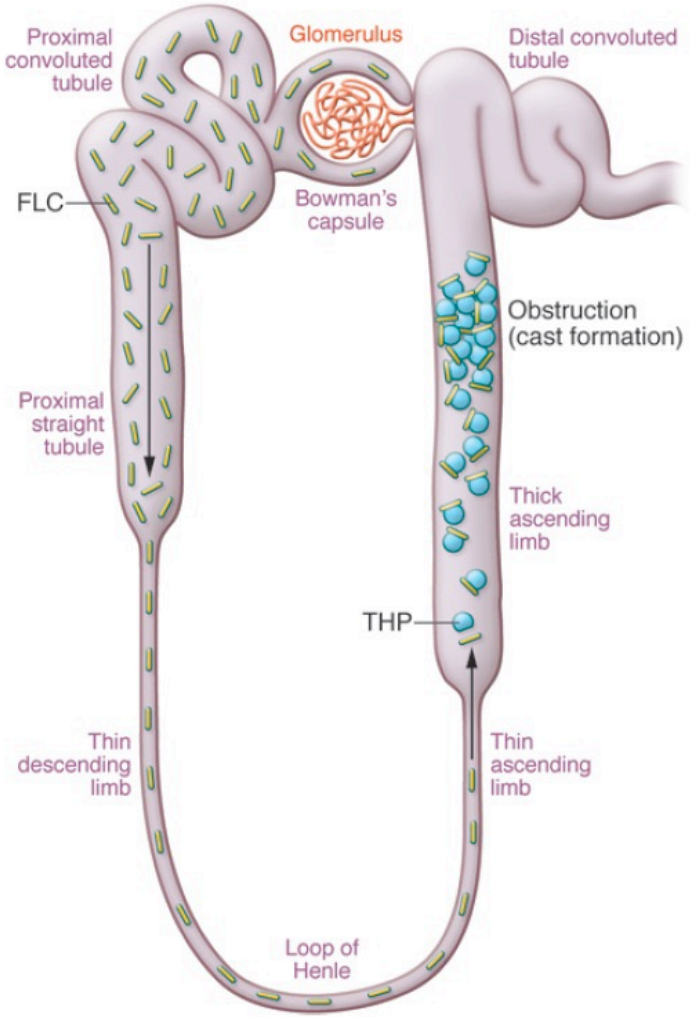


GLOMERULUS



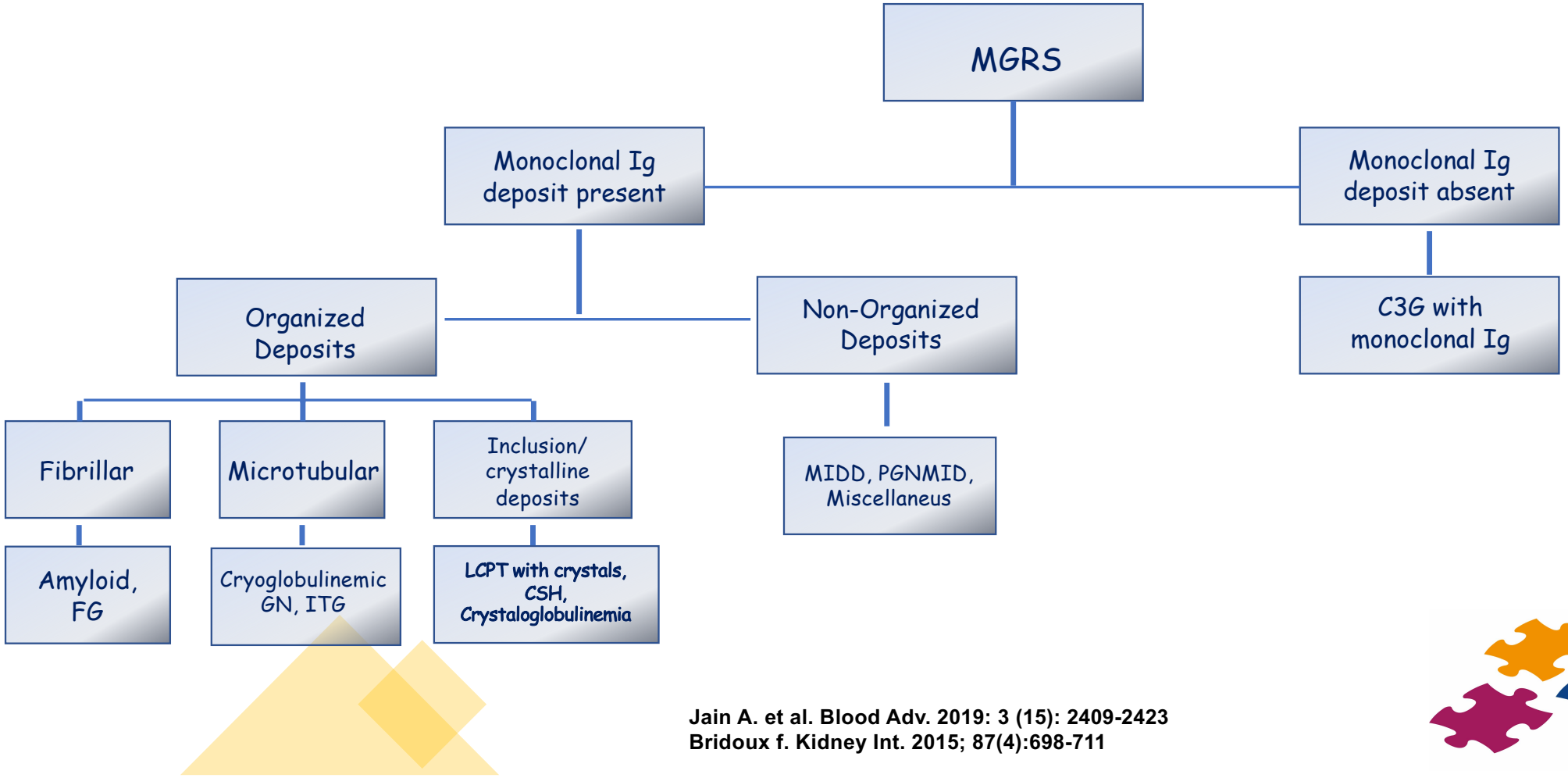
CAST Nephropathy





LIGHT CHAINS FORM CASTS WITH TAMM-HORSFALL GLYCOPROTEIN (UROMODULIN)

CLASSIFICATION OF MGRS BASED ON THE ULTRASTRUCTURAL FINDINGS OF THE MONOCLONAL DEPOSITS



Jain A. et al. Blood Adv. 2019: 3 (15): 2409-2423
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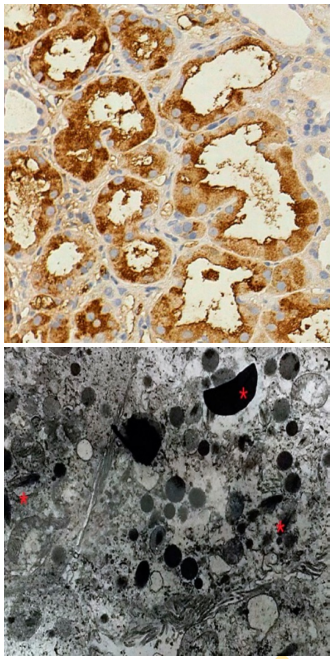
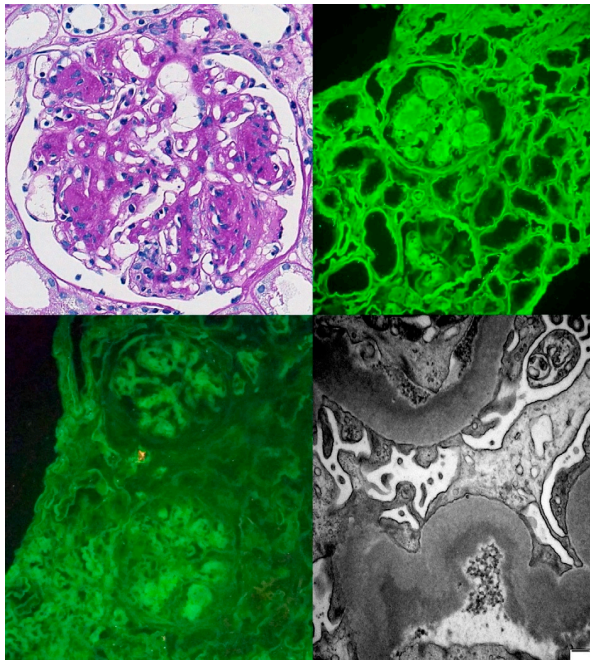
CLASSIFICATION OF MGRS BASED ON THE ULTRASTRUCTURAL FINDINGS OF THE MONOCLONAL DEPOSITS

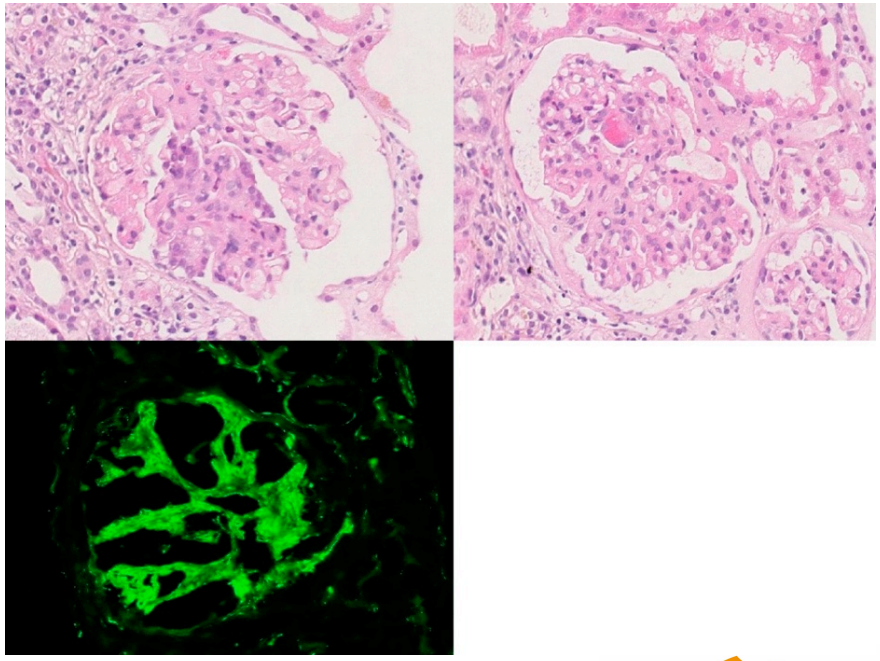
LCPT



LCDD



C3GN



Jain A. et al. Blood Adv. 2019: 3 (15): 2409-2423
Bridoux f. Kidney Int. 2015; 87(4):698-711

CLINICAL PRESENTATION

Clinical syndrome/presentation	Associated MGRS entities
NS	Amyloidosis (glomerular), MIDD
Nephritic-nephrotic syndrome (proteinuria, hematuria, hypertension, low complement levels, and renal insufficiency)	PGNMID, ITG, FG, C3G with monoclonal immunoglobulin, cryoglobulinemic GN
Acute renal failure	TMA, MIDD, and crystalglobulinemia
Proteinuria/progressive renal insufficiency	LCPT (with/without FS), MIDD, amyloidosis (tubulointerstitial and vascular), CSH, TMA

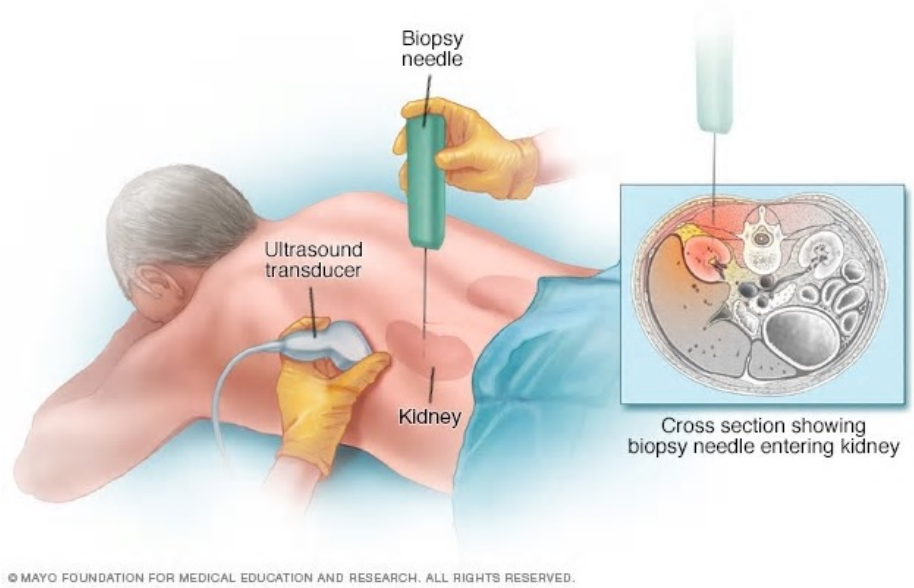
Adapted from Sethi et al[29] with permission.

Diagnosing MGRS: A CHALLENGE

- RENAL BIOPSY
- IDENTIFICATION OF PARAPROTEIN
- CLONAL IDENTIFICATION
- EXTRARENAL MANIFESTATIONS

DIAGNOSING MGRS: A challenge

Step 1. RENAL BIOPSY



Specimen must be processed

LIGHT MICROSCOPY

IMMUNOFLUORESCENCE
(Ab for light chains, heavy chains e intact Ig)

ELECTRONIC MICROSCOPY

DIAGNOSING MGRS: A challenge

Step 2-3. PARAPROTEIN and CLONAL IDENTIFICATION

DANGEROUS B CELL CLONE

→ **B-cell clone** (IgG/IgM)

→
- Flow cytometry on PB and BM aspirate.
- Biopsy and IHC for clonal markers
- CT scan ± PET-CT

PGNMID IN 70-80% DO NOT HAVE MG E/O CLONE

- n BM aspirate and biopsy
- T
- d or FDG-avid-LN
- cation
- testing

DANGEROUS LINFO-PLASMA CELL CLONE

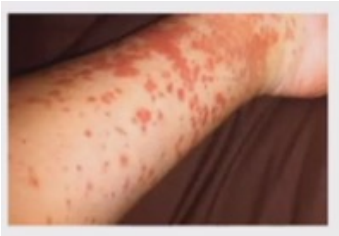
→ **Plasma cell clone** (IgG/IgA/IgM/IgD/IgE, sFLC)

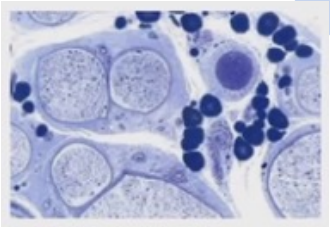
→
- Flow cytometry on BM aspirate and biopsy
- Cytogenetics and FISH testing.
- LDH, immunoglobulin levels
- Imaging (skeletal survey)

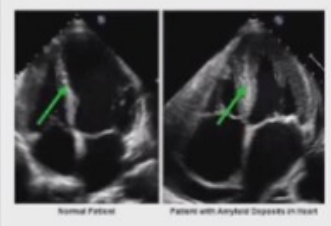
Adapted from Jain A et al. Blood Adv. 2019 Aug 13;3(15):2409-2423.

DIAGNOSING MGRS: A challenge

STEP 4. EXTRA-RENAL MANIFESTATIONS







Organ-directed testing based on the history and clinical examination findings:

- 2-dimensional echocardiogram, troponin level, N-terminal pro-BNP, cardiac magnetic resonance
- nerve conduction studies
- skin biopsy for cutaneous
- endoscopy and biopsy for gastrointestinal involvement.

IDENTIFICATION OF THE EXTRARENAL INVOLVEMENT SECONDARY TO THE MG IS CRITICAL FROM A THERAPEUTIC AND PROGNOSTIC PERSPECTIVE

Wechalekar AD, et al. Lancet. 2016;387(10038):2641-2654.
Merlini G. Hematology Am Soc Hematol Educ Program. 2017;2017:1-12.

SUMMARY I

- MGRS IS A CLONAL PROLIFERATIVE DISORDER WHICH PRODUCES A NEPHROTOXIC MONOCLONAL GAMMOPATHY THAT BY ITSELF DO NOT MEET CRITERIA FOR TREATMENT (MALIGNANCY)

- MGRS IS A "BENIGN" DISEASE WITH A POTENTIAL MALIGNANT

- THE DIAGNOSIS OF MGRS REQUIRES A KIDNEY BIOPSY TO DEMONSTRATE THE EFFECT OF MONOCLONAL GAMMOPATHY ON THE KIDNEY

Rate and predictors of finding monoclonal gammopathy of renal significance (MGRS) lesion on kidney biopsy in patients with monoclonal gammopathy

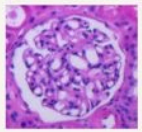
METHODS

MAYO CLINIC

Patients with monoclonal gammopathy

- Predictors of finding MGRS on kidney biopsy — Patients diagnosed between 2013-2018 (**n = 160**)
- Predictors of performing kidney biopsy in CKD patients with monoclonal gammopathy — Patients diagnosed between 2017-2018 (**n= 596**)
- **Excluded:** chronic dialysis, kidney transplant, hematologic conditions requiring treatment

RESULTS



MGRS : 40%

Most common: AL amyloidosis 43.8%

Non-MGRS: 60%

Most common: Arteriosclerosis 24.0%

Predictors of finding MGRS on kidney biopsy

- **Proteinuria ≥ 1.5 g/day** OR: 3.45 (1.43, 8.42)
- **Hematuria** OR: 2.94 (1.23, 7.01)
- **Abnormal free light chain ratio** OR : 11.04 (4.36, 27.91)

Predictors of performing Kidney biopsy

- **Age** OR: 0.97 (0.95, 0.99)
- **Serum creatinine** OR: 1.45 (1.10, 1.89)
- **24-hr urine protein** OR: 1.11 (1.0.3, 1.21)

CONCLUSION

Proteinuria ≥ 1.5 g/d, hematuria and abnormal FLC increase the likelihood of finding MGRS and a kidney biopsy should be highly considered in such patients

doi: 10.1681/ASN.2020010054

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

SUMMARY II

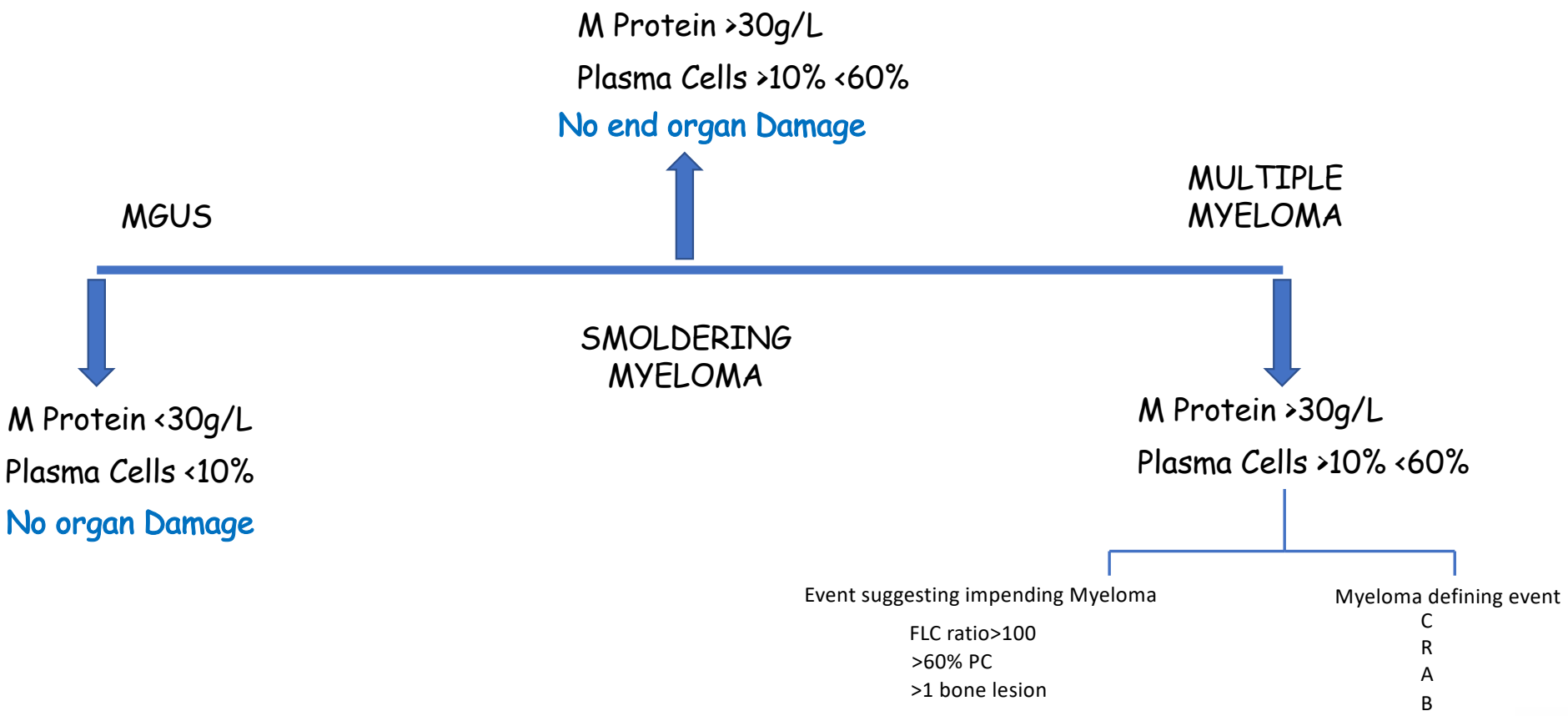
- 40% of MGUS WITH CHRONIC KIDNEY DISEASE DEVELOPE A MGRS

- PROTEINURIA >1.5g/24H, HEMATURIA and ABNORMAL FREE LIGHT CHAIN RATIO predict finding of MGRS at Kidney Biopsy

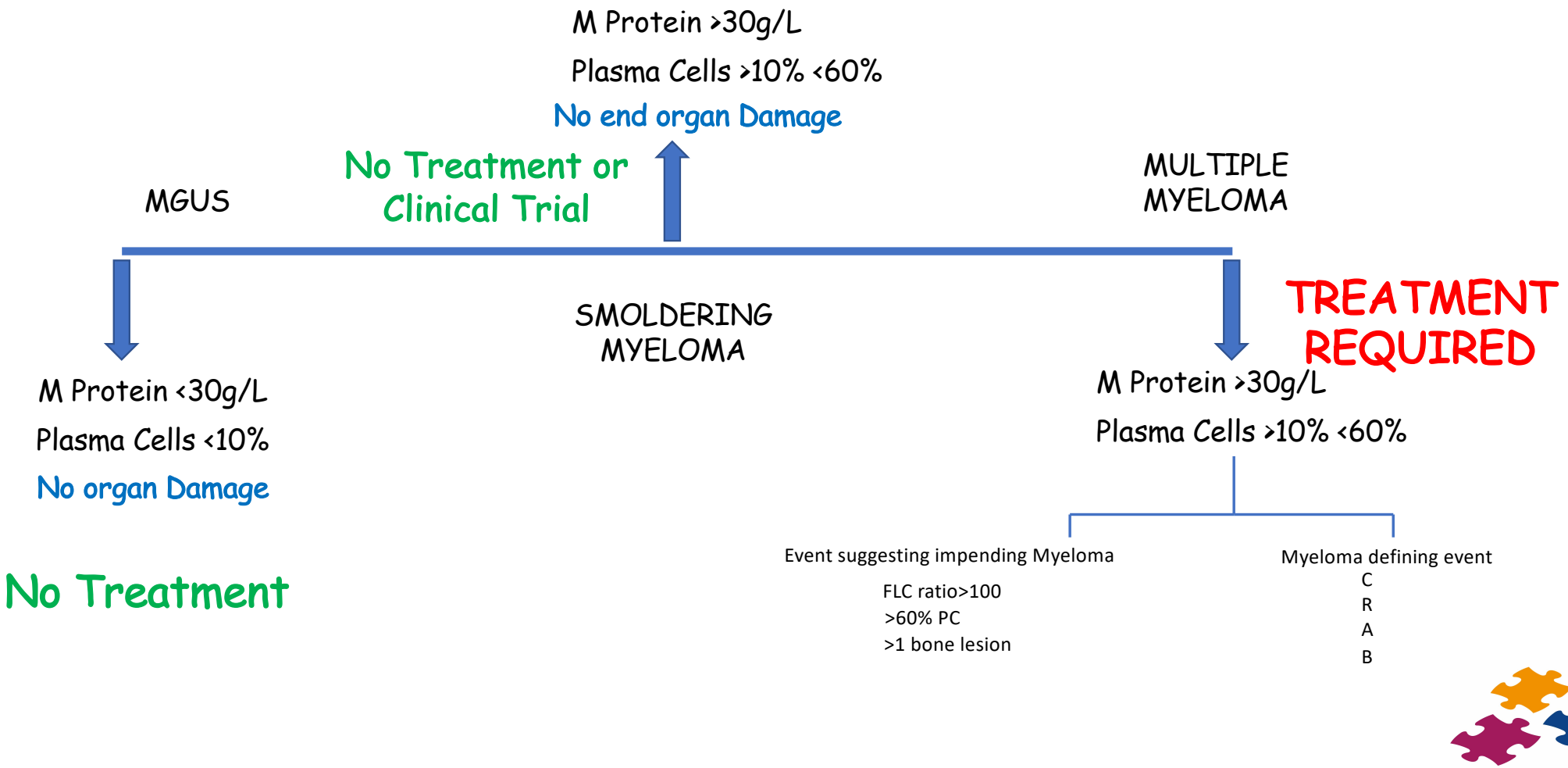
TREATMENT

IS TREATMENT ALWAYS NEEDED?

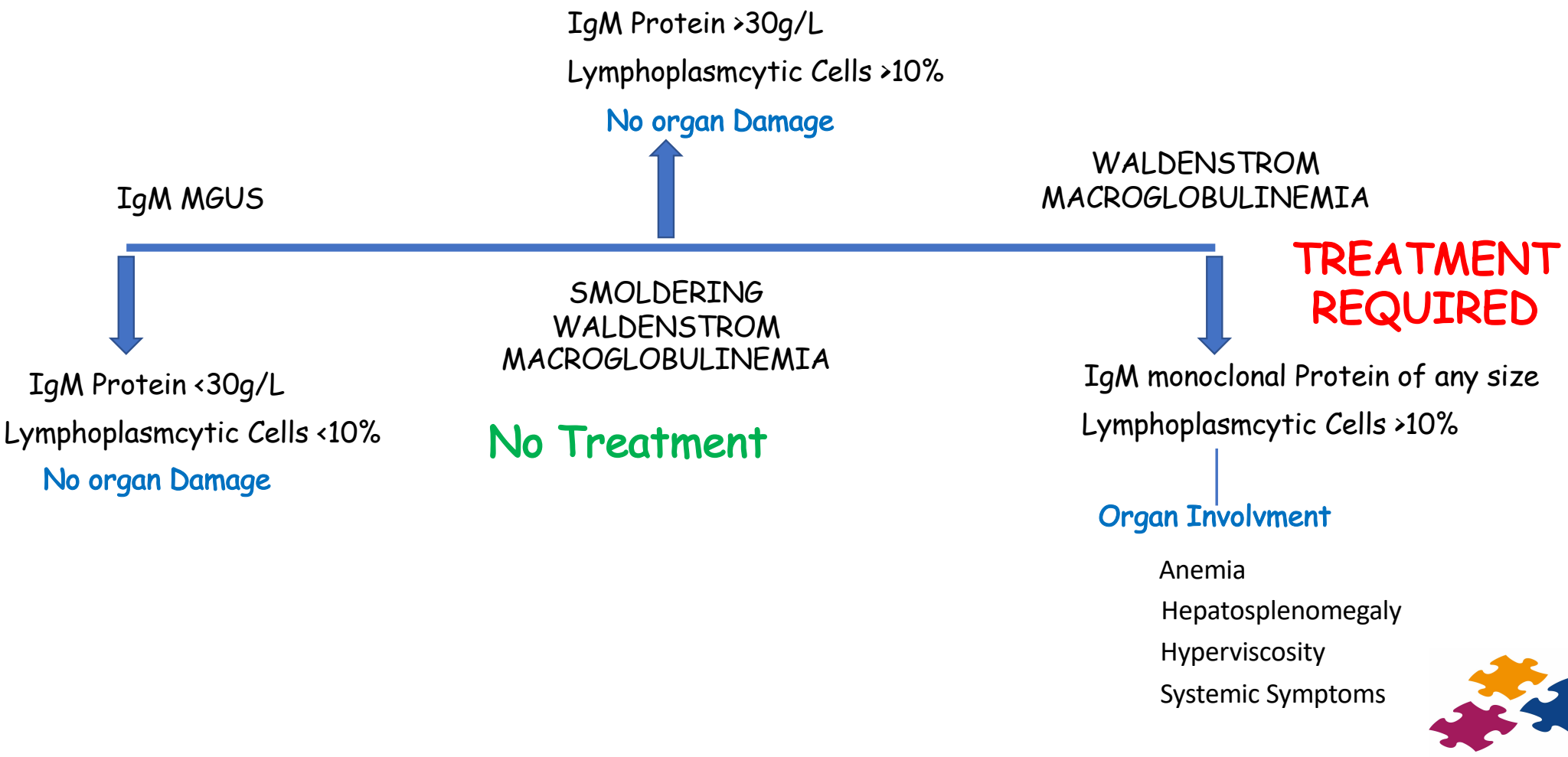
SPECTRUM OF DISEASE: Plasma Cell Clones



SPECTRUM OF DISEASE: Plasma Cell Clones



SPECTRUM OF DISEASE: Lymphoplasmcytic Clone



SPECTRUM OF DISEASE: B-Cell Clone

No Treatment

Monoclonal B-cell Lymphocitosis

Monoclonal B-cell $<5x10^9$

Persistent>3mo

TREATMENT REQUIRED stage III,IV

CRONIC LYMPHOCYTIC LEUKEMIA

Stage 0

Stage I,II

Stage III, IV

TREATMENT GOALS IN MGRS

- PRESERVATION OF RENAL FUNCTION
- IMPROVE LIFE EXPECTANCY (AL AMYLOIDOSIS)
- RESTORE ELIGIBILITY FOR KIDNEY TRANSPLANTATION
- MINIMIZE ADVERSE EFFECTS OFCHEMOTHERAPY

Leung N, et al. Blood. 2012;120(22):4292-4295.
Hogan JJ, et al. Clin J Am Soc Nephrol. 2016;11(9):1681-1691
Sayed RH,et al. Blood. 2015;126(26):2805-2810

PRINCIPLES WHILE TREATING MGRS

- **CKD STAGE 1-3:**

  EARLY INITIATION OF CHEMOTHERAPY IS INDICATED TO REDUCE THE PRODUCTION OF MONOCLONAL IMMUNOGLOBULIN AND ACHIEVE A DEEP HEMATOLOGICAL RESPONSE

- **CKD STAGE 4** OR **END-STAGE RENAL DISEASE:**

  CHEMOTHERAPY IS INDICATED ONLY IF THEY ARE PLANNED FOR A RENAL TRANSPLANT OR IF COEXISTING EXTRARENAL INVOLVEMENT IS PRESENT (ESPECIALLY CARDIAC, LIVER, OR PULMONARY)

- BASELINE **GLOMERULAR FILTRATION RATE** IS PROGNOSTIC FOR PREDICTING RENAL OUTCOME:
  PROMPT INITIATION OF THERAPY IS RECOMMENDED
  BEFORE IRREVERSIBLE RENAL DAMAGE OCCURS

TREATMENT AND OUTCOME

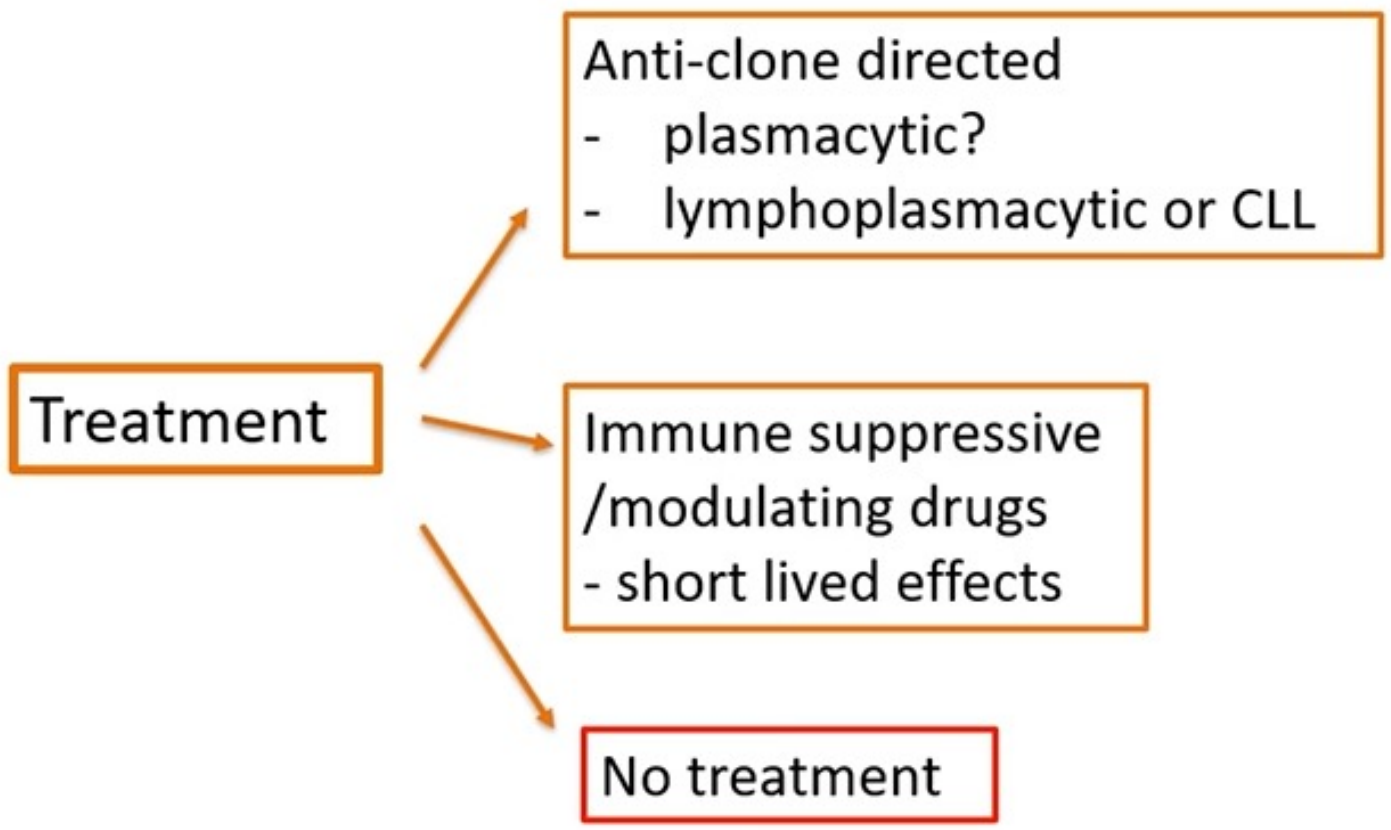
TREATMENT IS BASED ON A COMBINATION OF CHEMOTHERAPEUTIC AGENTS USED TO TREAT PCD OR NHL OPTIMIZING FOR SAFETY IN THE SETTING OF RENAL FAILURE, AS WELL AS EXTRARENAL INVOLVEMENT (ESPECIALLY CARDIAC).

TREATMENT IS DETERMINED BY:

- THE PATHOLOGICAL TYPE OF RENAL INJURY
- THE NATURE OF THE CLONE (B-CELL OR PLASMA CELL) THAT IS PRODUCING THE NEPHROTOXIC MONOCLONAL IMMUNOGLOBULIN
- THE LIKELIHOOD OF REVERSING EXISTING RENAL DAMAGE OR PREVENTING FURTHER RENAL INJURY.

Leung N, et al. Blood. 2012;120(22):4292-4295.
Hogan JJ, et al. Clin J Am Soc Nephrol. 2016;11(9):1681-1691
Sayed RH,et al. Blood. 2015;126(26):2805-2810

TREATMENT AND OUTCOME



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Sayed RH,et al. Blood. 2015;126(26):2805-2810

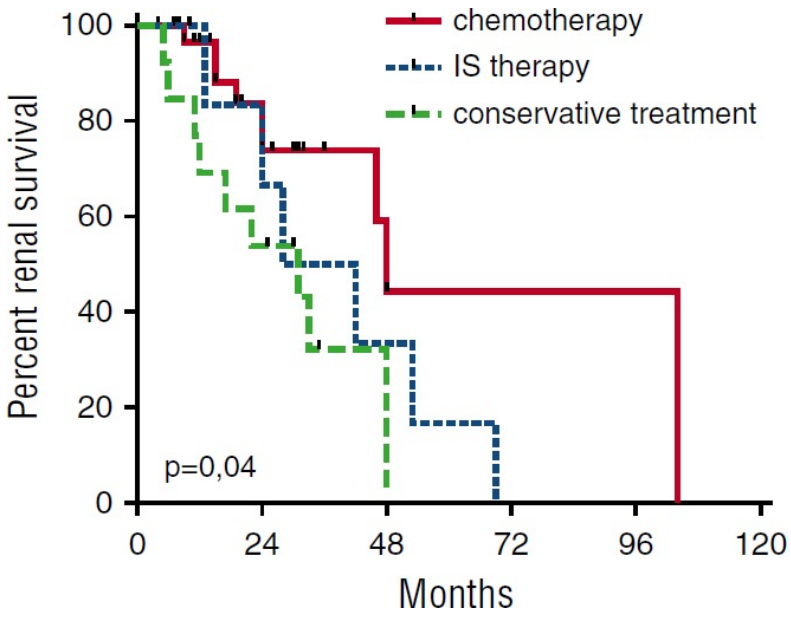
MGRS: TREATMENT SHOULD TARGET THE PATHOLOGIC CLONE

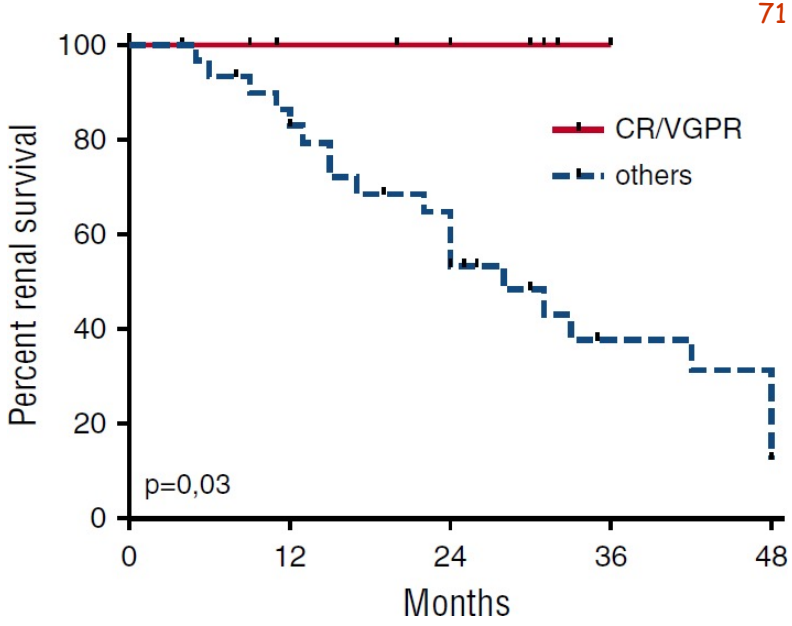
- BORTEZOMIB-BASED REGIMENS for plasma cell clones (VCD, Bort/Dex): bortezomib is safe in patients, no dose adjustment needed, may reduce inflammation
- RITUXIMAB-BASED THERAPIES for B-cell/lymphoma clones (Rituximab has proven efficacy, good toxicity profile)
- AUTOLOGOUS TRANSPLANT may be considered in selected patients

Leung N, et al. Blood. 2012;120(22):4292-4295.
Hogan JJ, et al. Clin J Am Soc Nephrol. 2016;11(9):1681-1691
Sayed RH,et al. Blood. 2015;126(26):2805-2810

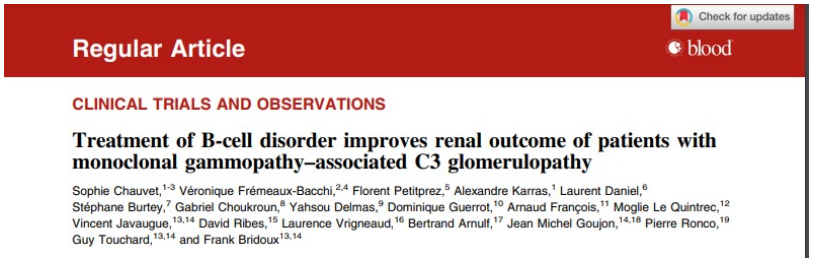
TREATMENT OF B-CELL DISORDER IMPROVES RENAL OUTCOME OF PATIENTS WITH MGRS

71 treated pts





DEEP AND PROLONGED HEMATOLOGICAL RESPONSE CAN LEAD TO ORGAN RECOVERY



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Regular Article

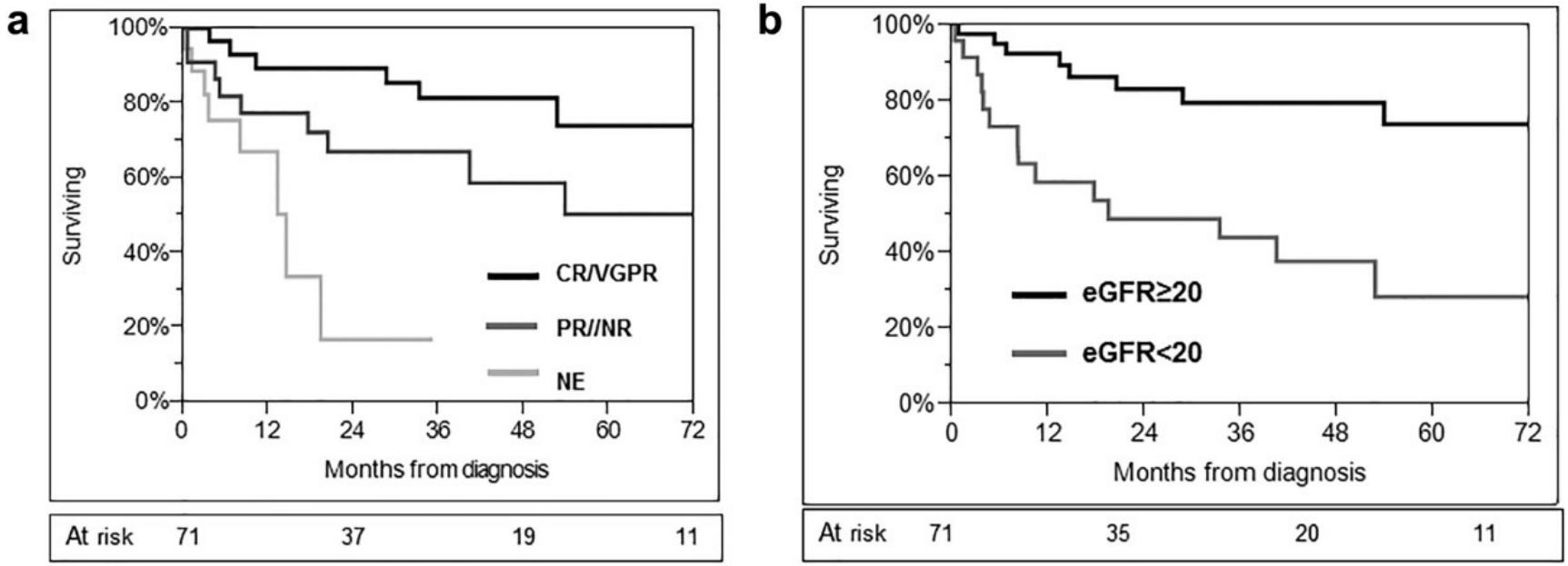
blood

CLINICAL TRIALS AND OBSERVATIONS

Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy–associated C3 glomerulopathy

Sophie Chauvet,[1-3] Véronique Frémeaux-Bacchi,[2,4] Florent Petitprez,[5] Alexandre Karras,[1] Laurent Daniel,[6] Stéphane Burtey,[7] Gabriel Choukroun,[8] Yahsou Delmas,[9] Dominique Guerrot,[10] Arnaud François,[11] Moglie Le Quintrec,[12] Vincent Javaugue,[13,14] David Ribes,[15] Laurence Vrigneaud,[16] Bertrand Arnulf,[17] Jean Michel Goujon,[14,18] Pierre Ronco,[19] Guy Touchard,[13,14] and Frank Bridoux[13,14]

TREATMENT OF B-CELL DISORDER IMPROVES OVERALL SURVIVAL



CR: complete response, NE: not evaluated, NR: no response,
PR: partial response, VGPR: very good partial response

DEEP AND PROLONGED HEMATOLOGICAL RESPONSE CAN LEAD TO BETTER OVERALL SURVIVAL

Taxiarchis V et al American Journal of Hematology, 2016

RESPONSE ASSESSMENT IN MGRS IS CHALLENGING

- PARAPROTEIN: In patients who have a detectable MG, may be followed up for hematological response assessment based on the IMWG criteria

- RENAL FUNCTION: In cases lacking a detectable baseline paraprotein, patients may be followed up using proteinuria and renal function (creatinine)

Palladini G, et al. J Clin Oncol. 2012;30(36):4541-4549.
Hogan JJ, et.al. Clin J Am Soc Nephrol. 2016;11(9):1681-1691.

HEMATOLOGICAL RESPONSE

Multiple Myeloma Model

Response Subcategory	Response Criteria
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow
sCR	CR as described above, plus: normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
VGPR	Serum and urine M-protein detectable by immunofluorescence but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours
PR	≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200mg 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 the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
SD	Not meeting criteria for CR, VGPR, PR or progressive disease

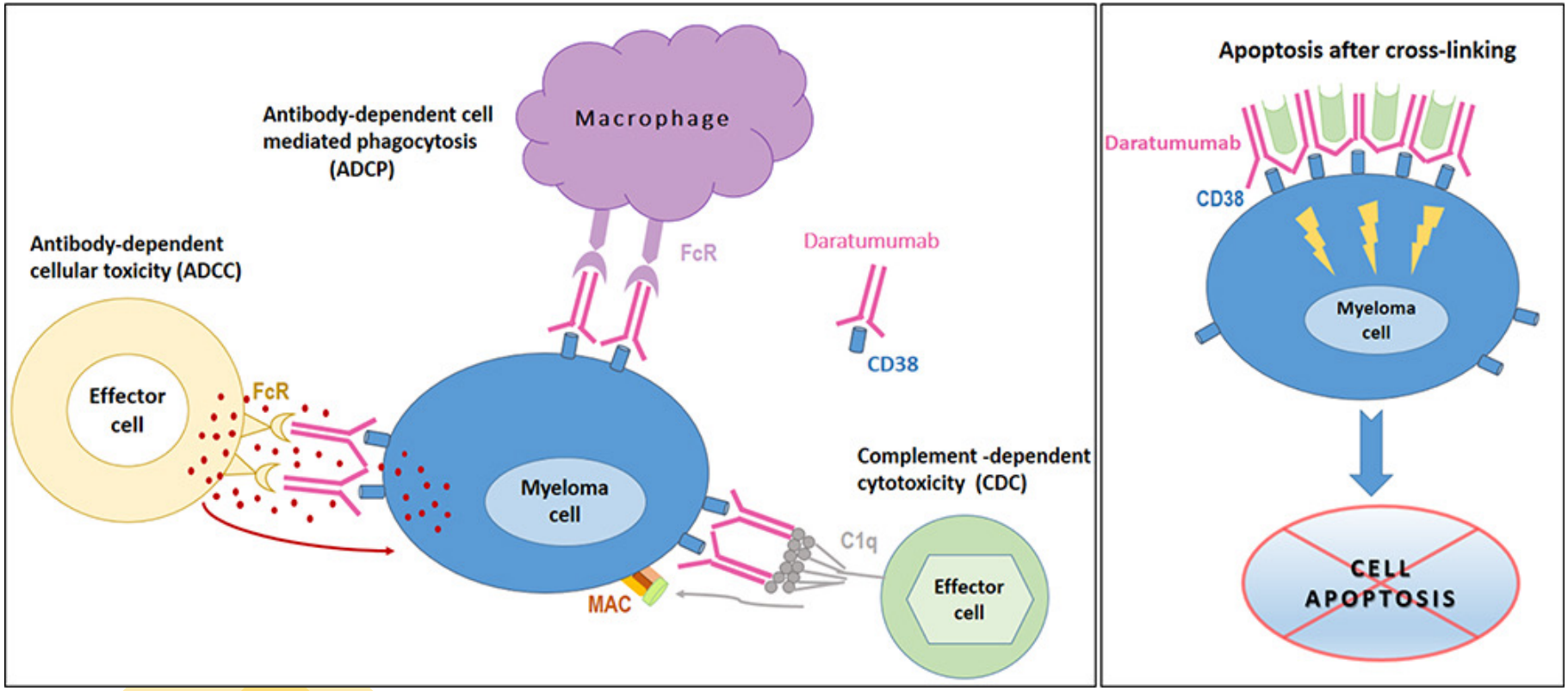
RENAL RESPONSE

Multiple Myeloma – Amyloidosis Model

Renal Response	Baseline eGFR, mL/min/1.73 m^2*	Best CrCl Response
Complete response	< 50	≥60 mL/min
Partial response	< 15	30-59 mL/min
Minor response	< 15	15-29 mL/min
	15-29	30-59 mL/min

Hematologic response	**Definition**
Complete response (CR)	Negative serum and urine immunofixation and normal FLC ratio
Very good partial response (VGPR)	dFLC <40 mg/L
Partial response (PR)	dFLC decrease >50% compared to baseline
low-dFLC response*	dFLC <10 mg/L
Cardiac response	**Definition**
Pre-treatment NT-proBNP ≥650 ng/L	Decrease of NT-proBNP by >30% and 300 ng/L
Pre-treatment NYHA class III or IV	At least 2 points decrease of NYHA class
Renal response	**Definition**
Pre-treatment proteinuria >0.5 g/24h	At least 30% decrease in proteinuria or drop below 0.5 g/24 hour

WHAT ABOUT DARATUMUMAB?

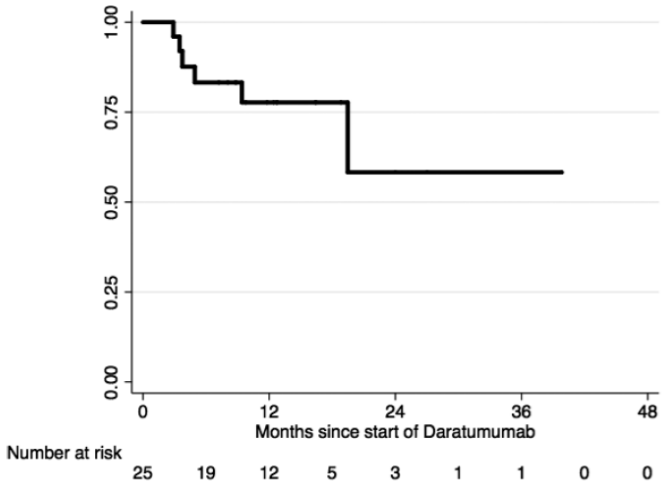


bjh research paper

Daratumumab-based therapy for patients with monoclonal gammopathy of renal significance

- 25 MGRS patients were treated with Dara-based regimes at standard dose (Dara alone, Dara-VCD and Dara-RD)
- The haematological response rates were: CR (22%), VGPR (22%)and PR (30%) with on ORR of 74%
- The toxicity was mild and predictable

TIME TO PROGRESSION
(hematologic relapse, subsequent therapy, dialysis or death)



OVERALL, DARA-BASED THERAPY IS AN OPTION FOR MGRS PATIENTS

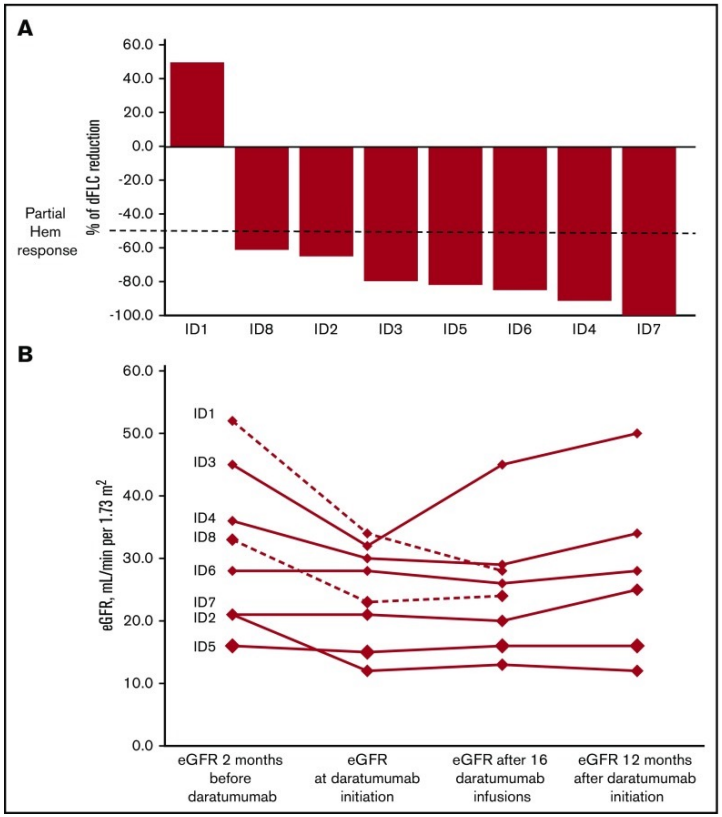
Kastris E. et al. Br J Haematol. 2020

EXCEPTIONAL CASE REPORT

blood advances

Daratumumab in light chain deposition disease: rapid and profound hematologic response preserves kidney function

- 8 LCDD patients (all refractory to last line of therapy)
- Treatment induded Dara alone or Dara-VD
- Changes in dFLC after 8 infusions of daratumumab showed higher rate of resonses (panel A)
- In all patients at least a PR was reached after starting therapy. Moreover, a suboptimal renal response was all achieved in all treated patients (panel B)
- Overall, Dara-based therapy is an option for R/R LCDD patients



Milani P. et al. Blood Advances 2020

Supportive care:

- prevention of thrombotic and infectious risk in pts with nephrotic syndrome
- treatment of hypertension and proteinuria with renin-angiotensin system inhibitors
- prevention of osteomalacia (FS) with bicarbonate, phosphate and vitamin D supplementation

Renal transplantation:

- MGRS should not be considered a controindication to renal transplantation although the risk of recurrence and graft loss is high
- must be discussed in each individual case, taking into account underlying MGRS characteristics, initial therapeutic response, presence of extrarenal manifestations, and patient's status
- clear counseling about risk of graft loss, its link with the B-cell clone and the potential need for reintroduction of chemotherapy

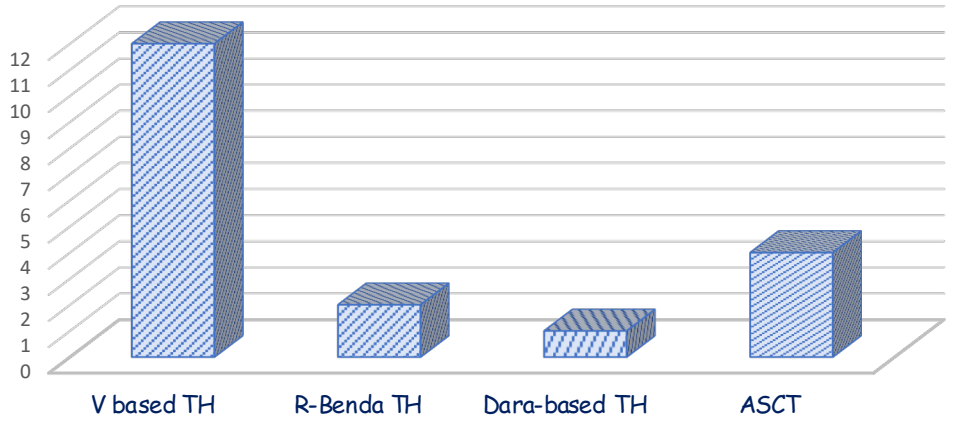
MGRS diagnosed 2018-2021

n. 15 (12 M and 3 F)

Median age: 59y

SEX	AGE	KIDNEY BIOPSY	TYPE	1ST LINE THERAPY	2ND LINE THERAPY
M	52	LCDD	IgA lambda	VCD (ASCT)	NO
F	59	MIDD	IgA lambda	VCD (ASCT)	NO
M	84	LCDD	IgA lambda	VD	NO
M	66	PGNMID	IgM lambda	R-Benda	NO
M	31	LCDD	IgG kappa	VCD (ASCT)	NO
F	61	AL	IgG lambda	VCD	NO
M	63	PGNMID	IgG kappa	VCD	VD
M	82	AL	IgA lambda	VD	NO
M	72	LCDD	IgM kappa	R-Benda	NO
M	52	AL	FLC kappa	VCD	NO
M	77	AL	IgA lambda	Dara-VMP	NO
M	59	AL	IgM lambda	VCD	R-benda
M	58	AL	FLC lambda	VCD (ASCT)	NO
F	51	AL	IgG lambda	VCD	NO
M	55	AL	IgG kappa	VCD	Revlimid

THERAPY



MGRS diagnosed 2018-2021

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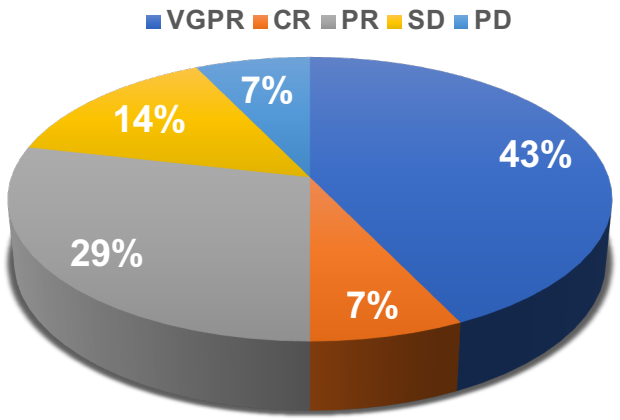
Median age: 59y

TYPE OF RESPONSE



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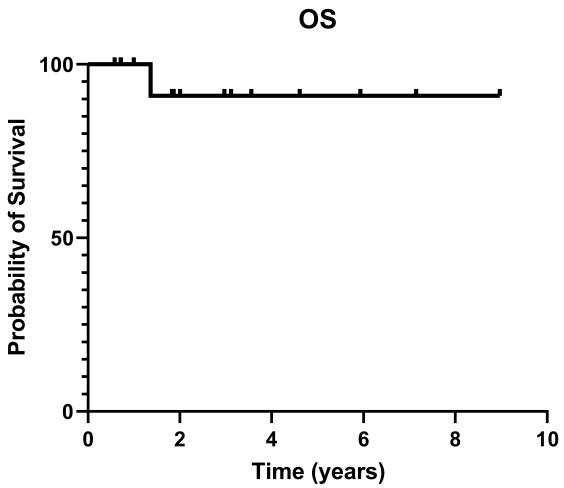

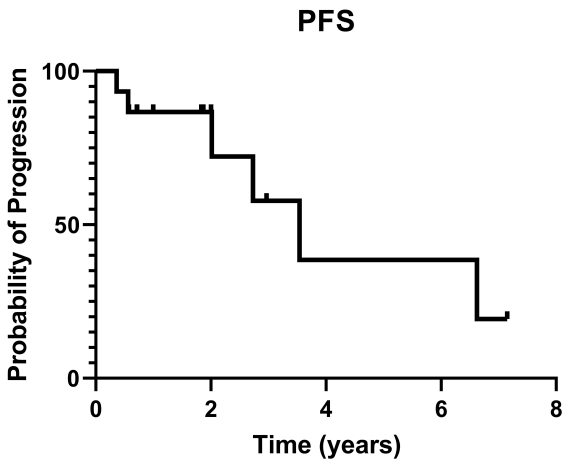

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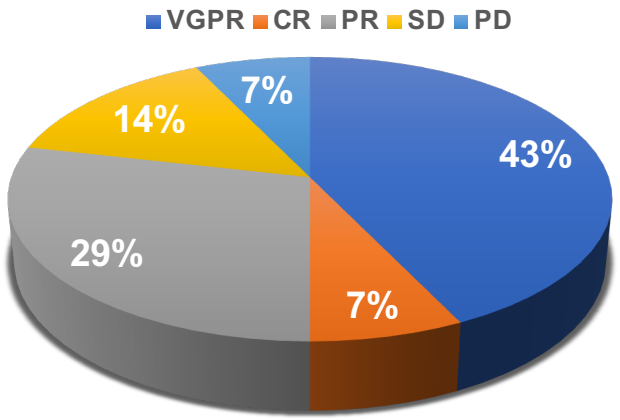

SUMMARY II

- TREATMENT FOCUSES UPON ERADICATION OF THE PATHOLOGIC MGRS CLONE
- RENAL RESPONSE REQUIRES A HEMATOLOGIC RESPONSE OF VGPR OR BETTER
- IMPROVEMENT IN PROTEINURIA AND/OR CREATININE SHOULD ACCOMPANY THE HEMATOLOGIC RESPONSE
- THERAPY SHOULD BE CONSIDERED IN ALL PATIENTS WITH EARLY DAMAGE TO AVOID/REDUCE THE RISK OF ESRD (OR INCREASE LIFE EXPECTANCY AS IN AL)
- THERAPY IN PATIENTS WITH ESRD DUE TO MGRS SHOULD BE CONSIDERED IN ORDER TO AVOID EXTRA-RENAL COMPLICATIONS OR RELAPSE AFTER RENAL ALLOGRAFT

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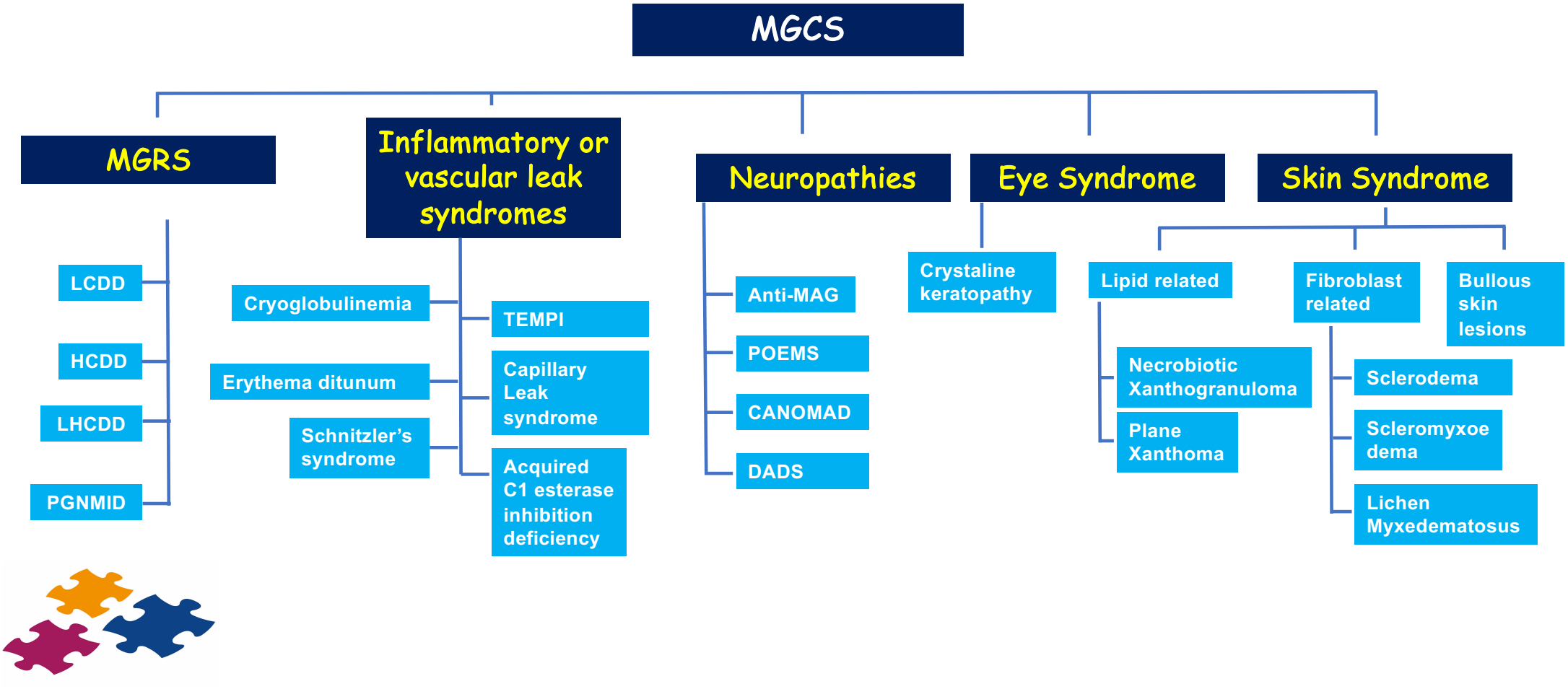
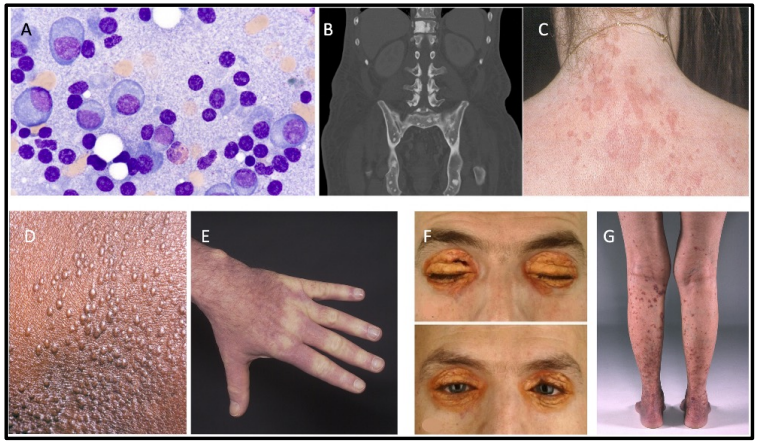
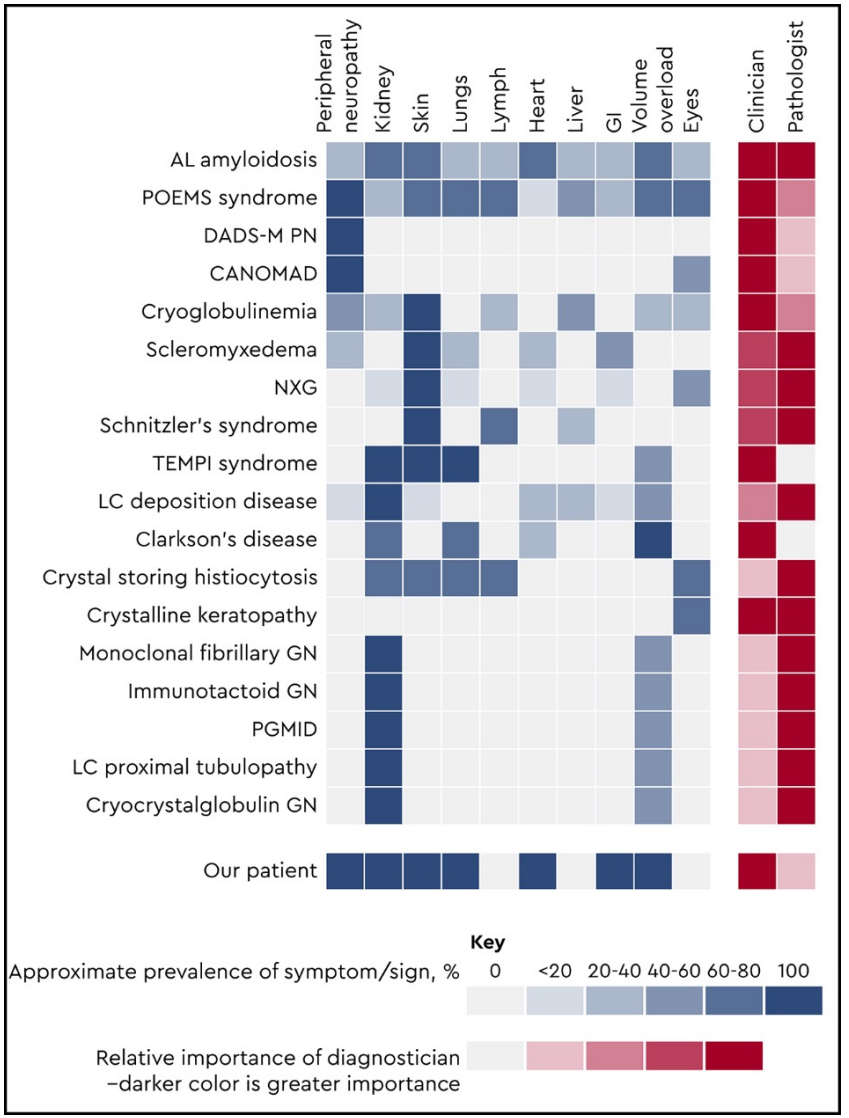
MONOCLONAL GAMMOPATHIES OF CLINICAL SIGNIFICANCE



MONOCLONAL GAMMOPATHIES OF CLINICAL SIGNIFICANCE





Dispenzieri A. Am Soc Hematol Educ Program, 2020

sex	age at diagnosis	Kidney Biopsy	Type of meas. disease	1st line therapy	2nd line therapy
M	52	LCDD	IgA lambda	VCD (ASCT)	NO
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F	51	AL	IgG lambda	VCD	NO
M	55	AL	IgG kappa	VCD	Revlimid