Nefropatie Correlate a Gammopatia Monoclonale

Francesco Piazza

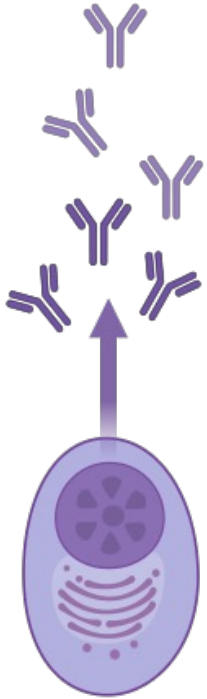
Dipartimento di Medicina -Università degli Studi di Padova

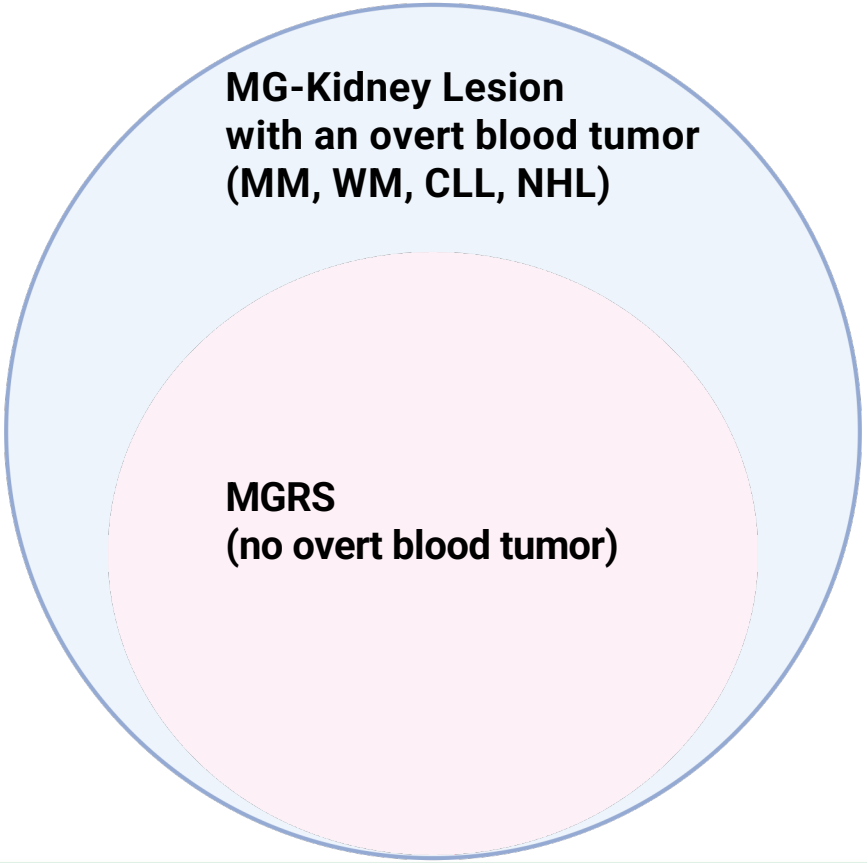
UOC di Ematologia-Azienda Ospedale Università Padova

Disclosures of Francesco Piazza

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			+			+	+
Roche			+			+	+
Kite Gilead	+		+			+	+
Takeda							
Janssen			+			+	+
Bejgene							+
Incyte			+			+	+

MG-Kidney Lesion

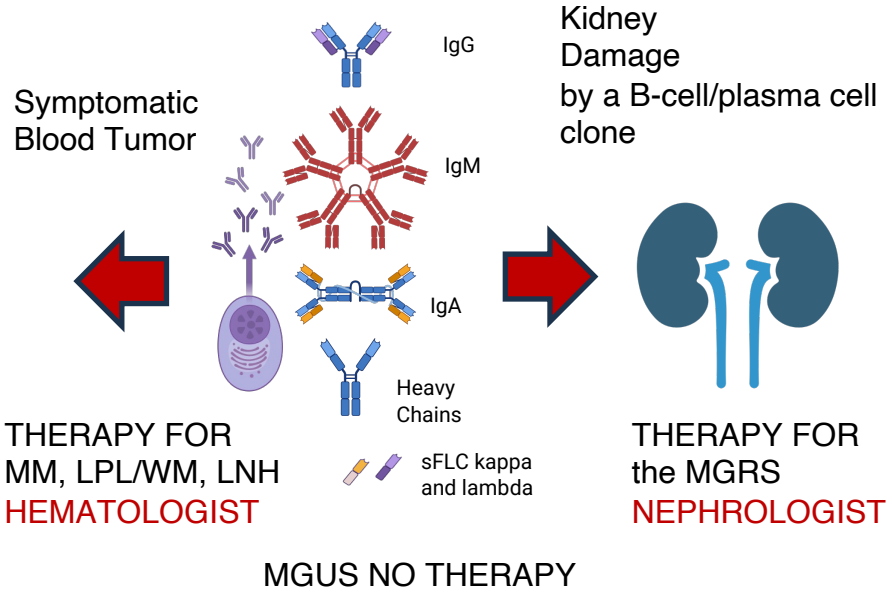




Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

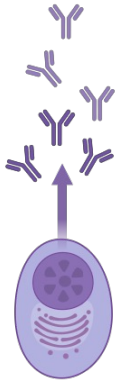
Nelson Leung,[1,2] Frank Bridoux,[3] Colin A. Hutchison,[4] Samih H. Nasr,[5] Paul Cockwell,[4] Jean-Paul Fermand,[6] Angela Dispenzieri,[2] Kevin W. Song,[7] and Robert A. Kyle,[2] on behalf of the International Kidney and Monoclonal Gammopathy Research Group

- **2012** the term MGRS (Monoclonal Gammopathy of Renal Significance) is coined by the ***International Kidney and Monoclonal Gammopathy Research Group (IKMG)***
- **Plasma and B-cell clonal** proliferative disorders that produce a nephrotoxic monoclonal Ig.
- Renal injury by a **nephrotoxic MC** without signs/symptoms of a symptomatic blood tumor (no diagnostic criteria met).
- Aside from some cases of amyloid light chain (AL) amyloidosis, **the diagnosis of MGRS requires a kidney biopsy**.
- Who **asks for treatment** is the **NEPHROLOGIST**



Leung N, Bridoux F, Hutchison CA, et al; International Kidney and Monoclonal Gammopathy Research Group. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant.
Blood. 2012;120(22):4292-4295.

Context – Definition: Monoclonal Gammopathy of Clinical Significance



Angela Dispenzieri, Monoclonal gammopathies of clinical significance, Hematology Am Soc Hematol Educ Program, 2020.

Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy–associated kidney lesions

Samih H. Nasr[1], Virginie Royal[2], Alejandro Best Rocha[3], Maike Büttner-Herold[4], Candice Roufosse[5], Frank Bridoux[6], Wesam Ismail[7], Lihong Bu[1], Lynn D. Cornell[1], Amélie Dendooven[8], Rajib K. Gupta[9], Shigeo Hara[10], Vincent Javaugue[6], Nicolas Kozakowski[11], Satoru Kudose[12], Gonzalo P. Méndez[13], Kimberley Oliver[14], Maria M. Picken[15], Dominick Santoriello[12], Sanjeev Sethi[1], Akira Shimizu[16], Geetika Singh[17], M. Barry Stokes[12], Su-xia Wang[18], Nelson Leung[19,20], Glen S. Markowitz[12] and Vivette D. D'Agati[12]

16 known MG-associated kidney lesions*.

- **22 variants** of known lesions.

Furthermore:

- ≥2 MG-associated kidney **lesions can coexist** in the same biopsy.
- Careful examination by **light microscopy, IF, and elctron microscopy**

***This term encompasses conditions characterized by either associated detectable:**

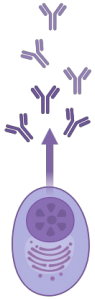
1) monoclonal Ig in the serum and/or urine, or

2) monotypic Ig deposits identified solely within the kidney.

Nasr SH et al. Kidney Int 2025

Lesions (N=16)	Variants (N=22)
Light chain cast nephropathy	Amyloidogenic
Ig-related amyloidosis	AL; AHL; AH
Monoclonal Ig deposition disease	LCDD; LHCDD; HCDD; LCDD (or LHCDD) by IF only
Proliferative GN with monoclonal Ig deposits	IgG; IgM; IgA; LC-only
Monoclonal membranous nephropathy	
Monoclonal immunotactoid glomerulopathy	Intact Ig; LC-only
Cryoglobulinemic GN	Type I; Type II
Intracapillary monoclonal IgM glomerulopathy	
C3 glomerulopathy associated with MG	C3GN; DDD
Heavy chain fibrillary GN	
Light chain proximal tubulopathy	Crystalline; Non-crystalline
Light chain crystalline podocytopathy	
Light chain crystal-storing histiocytosis	Interstitial; Glomerular
Crystalglobulin-induced nephropathy	
Crystalline cryoglobulinemic GN type I	
Thrombotic microangiopathy associated with MG	

Monotypic and Monoclonal



MGUS in the serum and/or urine may or may not* be detected

Monotypic: restricted heavy chain and/or light chain Ig staining in the kidney tissue.

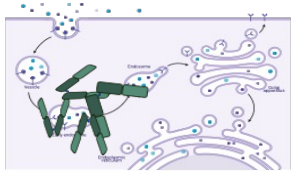
Monoclonal: can be determined upon demonstration of unique VL and VH sequences.

*As is the case for most (> 70%) cases of Proliferative GN with monoclonal Ig deposition – IgG and monoclonal membranous nephropathy

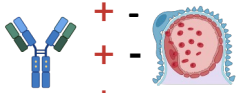
MGRS: pathophysiology

Misfolding of a fragment of mIg light chain >>> toxic **amyloid** fibers.

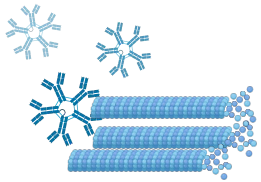
Ig light chain mutations in the V domain >>>resistance to proteolysis >>>accumulation in proxymal tubular cells as crystals: **Ligh Chain Proxymal Tubulopathy.**



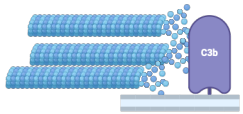
Hydrophobic residues, abnormal **glycosylation**, **positive charge** in the V domain >>> aggregation and deposition in the mesangium and along the negatively charged glomerular and tubular basement membranes. Also, monoclonal free Heavy Chains may deposit if unable to associate with light chains due to deletion of the first constant domain: **Monoclonal Ig Deposition Disease.**



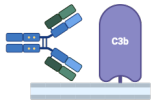
When **cryoglobulins precipitate** at cold temperature they form organized substructures (microtubules or crystals) >>> occlusion/inflammation of small arterioles and capillaries within glomeruli>>> **microtubular deposits.**



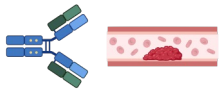
Non cryoglobulin microtubular deposits characteristic in **Immunotactoid Glomerulonephritis**. Classical complement pathway can also be activated >>> inflammation/endocapillary proliferation.

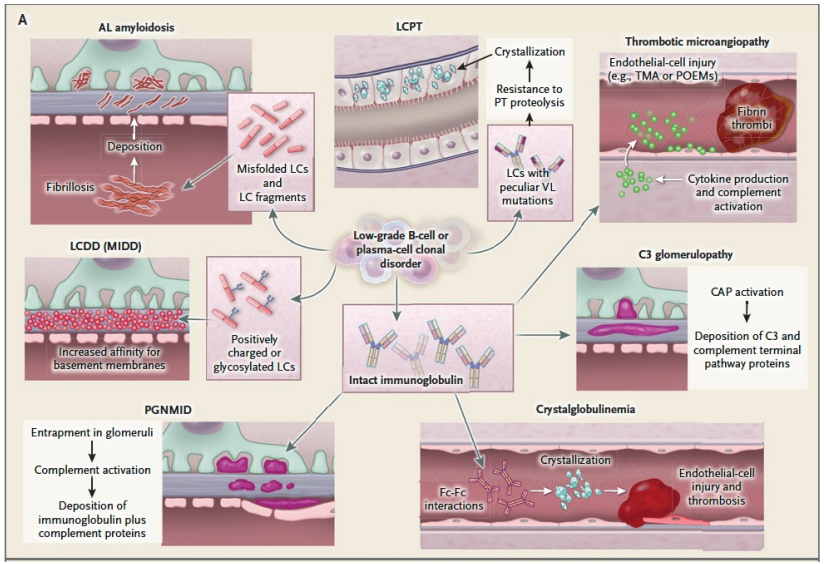


Activation of Complement Alternative pathway >>> **C3 deposition without mIg**.



Activation of thrombotic microangiopathy without mIg.





Leung N et al NEJM 2021

ULTRASTRUCTURE

Organized Ig deposits

Fibrils

AL, AH, AHL amyloidosis

Microtubules

- ITGP
- Cryo GN Type I & II

Crystals

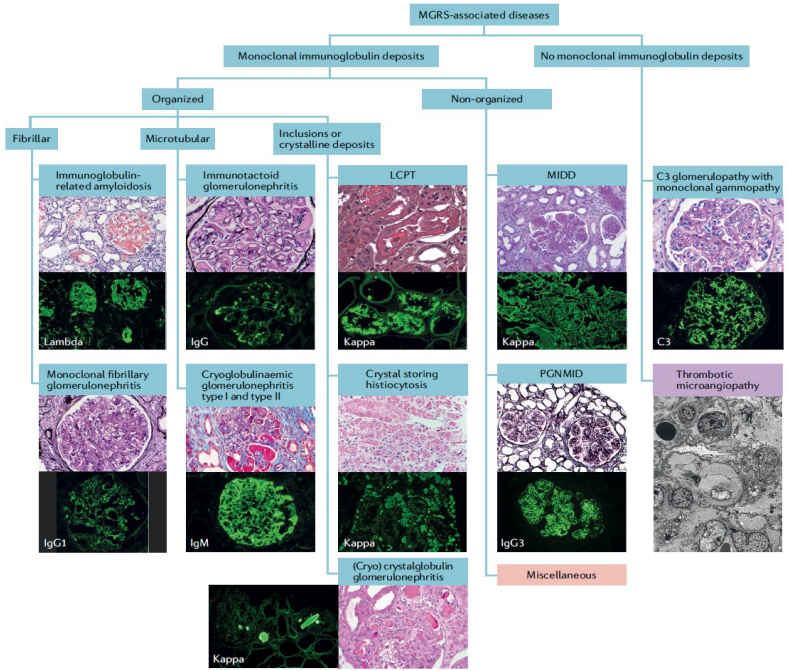
- LCPT/CSH Crystal and
- Cryo-crystal globulin GN
- LC crystalline podocytopathy

Non-organized Ig deposits

- MIDD (LCDD, HCDD, LHCDD)
- PGNMID
- Miscellaneous

No Ig deposits

- C3GP with monoclonal gammopathy
- TMA with monoclonal gammopathy



Bridoux F et al. Hematology 2024 ASH Edu
Leung N Nat Rev Nephrology 2019

CLINICAL CATEGORIES

Acute renal failure

- Cast nephropathy
- TMA
- RPGN

Chronic kidney disease

Nephrotic syndrome

- Amyloidosis
- MIDD

Nephritic-Nephrotic syndrome RPGN

- PGNMID
- Cryoglobulinaemic GN
- C3-glomerulopathy
- Immunotactoid glomerulopathy

Proteinuria progressive CKD

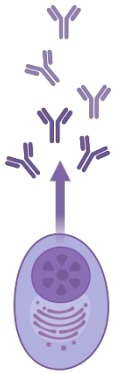
- MIDD
- Light chain proximal tubulopathy
- Amyloidosis
- Cristal storing histiocytosis
- TMA
- Other

Challenges in MGRS management

- The **mean age of patients with MGRS exceeds 60 years**.
  - chronic kidney disease (CKD) and MGUS are prevalent in an elderly population.
  - Diagnosing MGRS is thus like **searching for the proverbial needle in a haystack**.
  - **Avoid underdiagnosis** (missing MGRS as a treatable disease)
  - **Limiting costs** (unnecessary diagnostic tests) and **without causing harm** (unnecessary diagnostic procedures such as kidney biopsy).
- **Heterogeneity** and **complexity**.
- Need of **EM**, **ancillary techniques** (**IF**, **IF on paraffin** tissue after protease digestion, **mass spectrometry**, **immunoelectron** microscopy).
- Many MGRS lesions (aside from AL amyloidosis and LCDD) are likely **underdiagnosed** >>> a substantial fraction of patients may not receive appropriate therapies
- ***Not all patients who have monoclonal gammopathy (MG) and chronic kidney disease (CKD) have MGRS, and the 2 may be present in a patient without direct correlation.***

Nasr SH et al. Kidney Intl 2025
Klomjit N et al. Kideny Intl 2025

Referral - Screening



MGUS >>> MGRS?

- serum creatinine
- estimated-glomerular filtration rate (eGFR)
- urinalysis for microscopic hematuria - proteinuria
- 24 hour urine protein

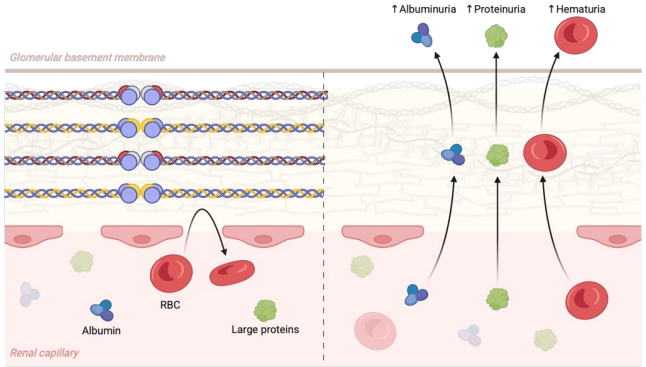
- **Microscopic hematuria**

- glomerulonephritis (especially if + proteinuria)

- **Albumin to creatinine ratio (ACR)**

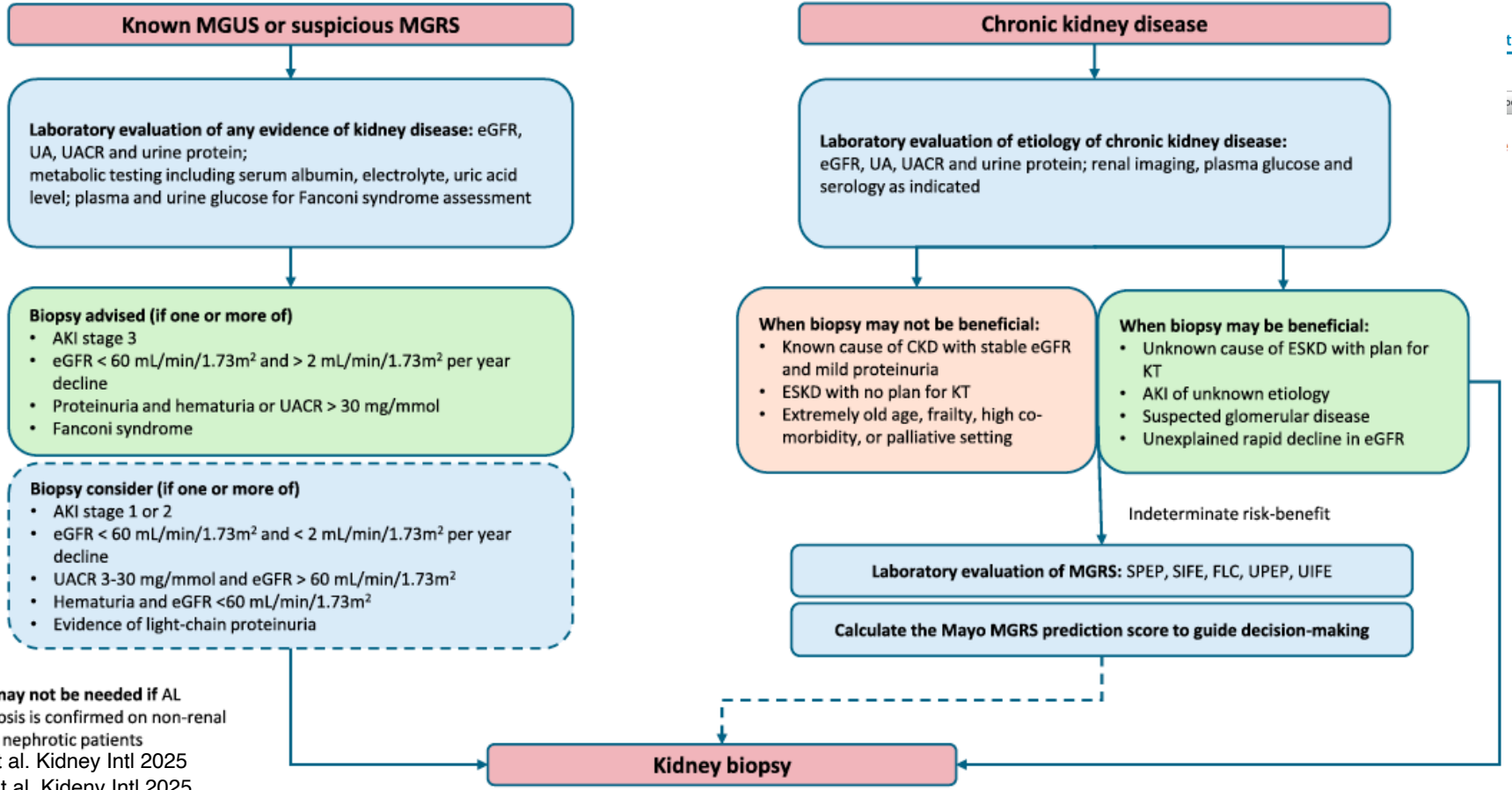
- If ACR > 30 mg/mmol + MGUS

- **Rapid deterioration of kidney function** (e.g. sGFR reduction of > 25% in 12 months)



Nasr SH et al. Kidney Intl 2025
Klomjit N et al. Kideny Intl 2025

Kidney Biopsy?



Nasr SH et al. Kidney Intl 2025
Klomjit N et al. Kideny Intl 2025

Therapy for MGRS

- Autologous Stem Cell Transplant (ASCT) should be considered in selected cases:

➢ AL amyloidosis
➢ PGNMID, C3 GN

- In End-stage Kidney Disease (CKD stage 3b-5; eGFR ≤ 20 ml/min/1.73m^2) clone-directed therapy should not be initiated (only supportive therapy). Therapy only if other systemic involvement is present or in cases with planned kidney transplant.

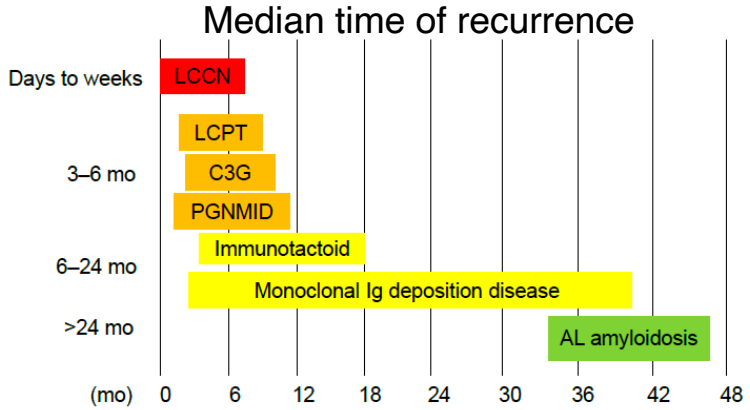
Leung N et al. Nat Rev Nephrol 2019
Leung N et al. ASH Educational 2024

meeting report www.kidney-international.org

Management recommendations for kidney transplantation in patients with plasma cell dyscrasia

Naoka Murakami[1], Christopher D. Blosser[2,3], Allison B. Webber[4], Gaurav Gupta[5], Neeraj Singh[6], Samhita Boppana[6], Samip Master[7], Ravipraseena Parasuraman[8], Erica L. Campagnaro[9], Anuja Java[1], Ben Sprangers[10,11], Bhavna Bhasin-Chhabra[12], Erik Lum[13], Diala Khirfan[14], Mariam P. Alexander[15], Miklos Z. Molnar[16], Brian Benes[17], Ajay Kumar Thakur[18], Naresh Bumma[19], Sabine Karam[20,21], Malin Hultcrantz[22], Frank Bridoux[23], Vaishali Sanchorawala[24], Nelson Leung[25] and Heather Landau[22]

- Therapeutic option re-evaluated given the improved overall and disease outcomes in MM.
- Eligible patients without severe extrarenal disease.
- Best results if hematologic CR prior to transplant.
- Elevated rate of post-transplant relapse >>> post transplant consolidation therapy.



Murakami N et al. Kidney Intl. 2025

IMWG
(International Myeloma Working Group)

- MGRS with tubular injury

Box 1. Hematologic Response Criteria for Multiple Myeloma

Stringent complete response
- Complete response (see below) plus normal sFLC ratio and absence of clonal plasma cells on bone marrow biopsy

Complete response
- Negative sIFE and uIFE, disappearance of plasmacytomas, <5% plasma cells on bone marrow biopsy

Very good partial response
- SPEP and UPEP negative but monoclonal protein detectable by sIFE or uIFE or >90% reduction in serum monoclonal paraprotein with urine monoclonal protein < 100 mg/24 h

Partial response
- >50% reduction in serum monoclonal protein, >90% reduction in 24-h urine monoclonal protein (or to <200 mg/24 h), >50% reduction in baseline plasmacytoma size (if present)
- If monoclonal protein is unmeasurable, >50% reduction in difference between involved and uninvolved FLC levels
- If FLC not measurable, >50% reduction in plasma cells in bone marrow from baseline (requires >30% plasma cells at baseline)

Minimal response
- 25%-49% reduction in serum monoclonal protein, 50%-89% reduction in 24-h monoclonal protein in urine
- 25%-49% reduction in size of plasmacytomas (if present)

Stable disease
- Does not meet criteria for any of response pattern above or for progressive disease

Progressive disease
- 25% increase from lowest response value in serum monoclonal protein (increase > 0.5 g/dL) and/or urine monoclonal protein (increase > 200 mg/24 h)

Note: Based on information in Kumar et al (International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17:e328-e346).

Abbreviations: sFLC, serum free light chain; sIFE, serum immunofixation; SPEP, serum protein electrophoresis; uIFE, urine immunofixation; UPEP, urine protein electrophoresis.

Renal Response

Table 1. Criteria for Renal and Hematologic Responses

Renal Response

International Society of Amyloidosis (Gertz et al,[30] 2005)	International Myeloma Workshop (Dimopoulos et al,[31] 2010)
≥50% decrease (≥0.5 g/d) of 24-h urine protein (urine protein must be >0.5 g/d pretreatment); Scr and creatinine clearance (or eGFR) must not decrease by 25% over baseline	Complete renal response: increase in baseline eGFR from <50 to ≥60 mL/min/1.73 m^2 Partial renal response: increase in baseline eGFR from <15 to 30-59 mL/min/1.73 m^2 Renal minor response: increase in baseline eGFR from <15 to 15-29 mL/min/1.73 m^2, or if baseline eGFR was 15-29, then increase to 30-59 mL/min/1.73 m^2

ISA
(International Society of Amyloidosis)

- MGRS with glomerular injury with proteinuria
- Valid also for assessing renal response

Box 2. Hematologic Response Criteria for AL Amyloidosis

Complete response
- Negative SPEP, sIFE, UPEP, uIFE, and normal sFLC ratio

Very good partial response
- dFLC < 40 mg/L

Partial response
- Decrease in dFLC by >50% (in patients with baseline dFLC > 50 mg/L)

No response
- Improvement in paraprotein levels but less than partial response

Progression
- From complete response: any detectable monoclonal protein or abnormal sFLC ratio (involved light chain must be at least double the normal range)
- From partial response: 50% increase in serum monoclonal protein to >5 g/dL or 5% increase in urine monoclonal protein to >200 mg/d
- At any time: sFLC increase of 50% to >100 mg/L

Note: Based on information in Palladini et al (New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol.* 2012;30(36):4541-4549).

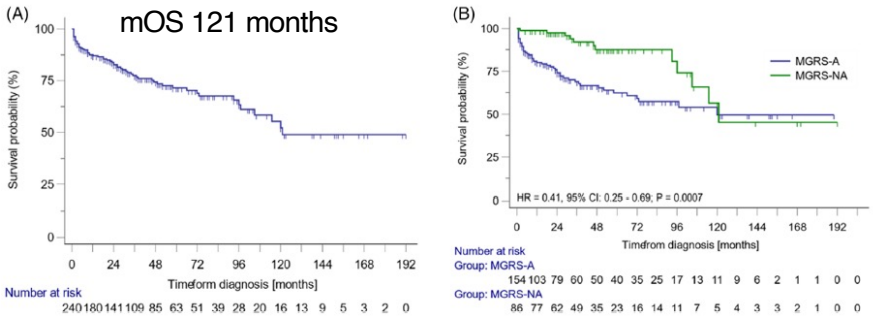
Abbreviations: dFLC, difference in free light chains (involved minus uninvolved light chain in serum); sFLC, serum free light chain; sIFE, serum immunofixation; SPEP, serum protein electrophoresis; uIFE, urine immunofixation; UPEP, urine protein electrophoresis.

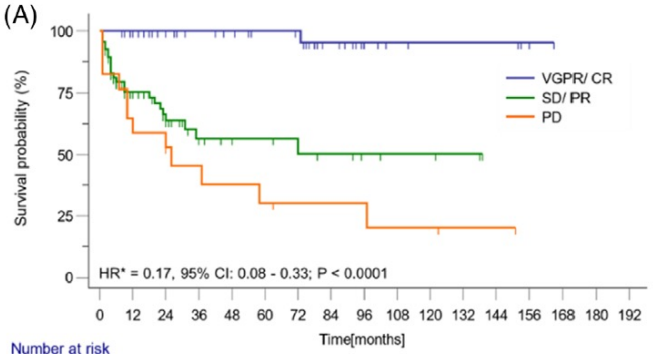
Received: 19 January 2022 | Revised: 14 March 2022 | Accepted: 1 April 2022
DOI: 10.1002/ajh.26566

RESEARCH ARTICLE

AJH WILEY

Monoclonal gammopathy of renal significance (MGRS): Real-world data on outcomes and prognostic factors





PROGNOSTIC FACTORS:

- β2 Microglobulin levels > 5.5 mg/L
- Age > 65 yrs
- Preexisitng renal function > 177 umol/L
- Dyalisis

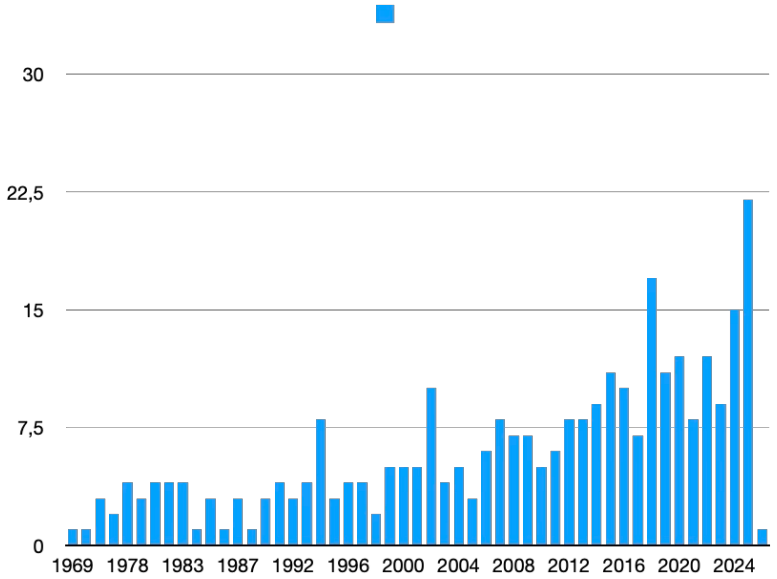
Gozzetti A et al. Am J Hematol 2022

Renal involvement in LPL/WM

- Relatively **rare**
- **Underrecognized** despite awareness
- Mechanisms **beyond MGRS**

>>MG-Kidney Lesions

- Clinically **impactful**
- Scarce literature



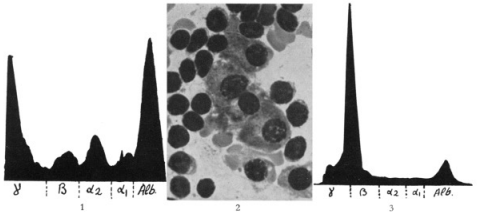
Pubmed articles for
«WM or Lympholasmocytic Lymphoma
And renal damage, dysfunction and MGRS»

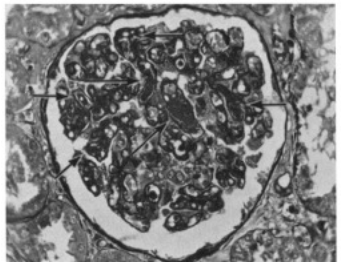
Macroglobulinemic Nephropathy*

Acute Renal Failure in Macroglobulinemia of Waldenström

I. Argani, M.D.† *and* G. F. Kipkie, M.D.
Kingston, Ontario

- First report of WM-related kidney injury
- Severe dehydration >>> AKI
- Biopsy revealed proteinaceous material in the glomerular capillaries





Argani I and Kipkie GF Am J Med 1964

N =16
5 biopsied
11 Autopsies

- 3 Amyloidosis
- 6 Interstitial infiltrate
- 6 Deposits + thrombi
- 1 no lesions

PATHOLOGY OF THE KIDNEY IN WALDENSTRÖM'S MACROGLOBULINEMIA*

Study of Sixteen Cases

LILIANE MOREL-MAROGER, M.D., ANDRÉ BASCH, M.D., FRANÇOISE DANON, M.D., PIERRE VERROUST, M.D., AND GABRIEL RICHET, M.D.

With the Technical Assistance of Anne-Marie Bouteiller

Table 2. Histologic Observations.

Case No.	Source of Tissue	Glomerular Lesion	Immuno-fluorescence	Interstitial Infiltration
1	Autopsy	Amyloidosis, very focal	*	–
2	Autopsy	Amyloidosis	*	+
3	Biopsy	Amyloidosis, very focal	No fixation	–
4	Biopsy & autopsy	No detectable lesion	Circulating IgM	–
5	Autopsy	No detectable lesion	*	+ (PAS-positive cells; reticular cells).
6	Autopsy	No detectable lesion	*	–
7	Autopsy	No detectable lesion	*	+++
8	Autopsy	No detectable lesion	*	++ tophus
9	Autopsy	No detectable lesion	*	++ (PAS-positive cells; intranuclear inclusions).
10	Biopsy	Endomembranous deposits	IgM +	+ (PAS-positive cells)
11	Autopsy	Rare deposits in glomerular capillaries & arterioles	*	++
12	Autopsy	Large thrombi in glomeruli & arterioles	*	+
13	Autopsy	Thrombi & deposits in glomerular capillaries & arterioles	*	+
14	Autopsy	Large thrombi + endomembranous deposits in glomerular capillaries, arterioles & tubules†	IgM +	+
15	Biopsy & autopsy	Thrombi + endomembranous deposits in glomerular capillaries†	IgM +	–
16	Biopsy	No detectable lesion	No fixation	–

*Not done.

†Slight endothelial proliferation.

Morel-Maroger L et al. NEJM 1970

Main retrospective studies:

1) **American-european series *(Vos et Al, BJH 2016)* of 1391 patients with WM of which 44 with demonstrated biopsy-proven disease localization (3,16%).**
2) **Mayo Clinic case series *(Higgins et Al, Clin J Am Soc Nephrol 2018)* of 1363 WM patients of which 42 positive for renal localization of disease (3,08%).**
3) **Other minor series(*Chauvet et al, Nie et Al..).***

Study	N°patients	N°renal biopsies	Inclusion criteria	Follow up time	Findings
Vos et Al, BJH 2016	1391	44	- ClCr < 60 ml/min and positive proteinuria - Positive kidney biopsy	1999-2015	- Clinical and histopathological description
Higgins et Al, Clin J Am Soc Nephrol 2018	1363	57	- serum monoclonal IgM - Positive bone marrow biopsy - Positive kidney biopsy	1996-2015	- Clinical and histopathological description
Chauvet et al, Am J Kidney Dis 2015	35	35	- serum monoclonal IgM - ClCr < 60 and/or proteinuria >0.5g/24h - Positive kidney biopsy	1992-2012	-

bjh research paper

Renal disease related to Waldenström macroglobulinaemia: incidence, pathology and clinical outcomes

DANA FARBER STUDY

- 1391 pts with WM.
- 52 cases (kidney biopsy proven): 8/52 unrelated causes; 44/52 due to WM
- **Est. cumulative incidence: 5.1% at 15 year**

Five main histologica patterns:

- ✓ **Amyloidosis 25%**
- ✓ **Monoclonal IgM DD/cryoglobulinemia 23%**
- ✓ **LPL infiltration 18%**
- ✓ LCDD 9%
- ✓ LC cast nephropaty 9%

Potentilally related to LPL/WM:

- ✓ **Thrombotic microangiopathy 7%**
- ✓ Minimal change disease 5%
- ✓ Membranous nephropathy 2%
- ✓ Crystal storing disease 2%

- ➢ Check for unexplained renal insufficiency/nephrotic syndrome with biopsy
- ➢ Pro-active surveillance to start early treatment

Vos JM et al BJH 2016

STUDIO MAYO CLINIC

1) IgM+ 2) BM biopsy+ 3) Kidney biopsy +

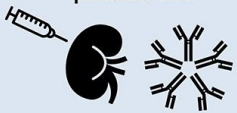
Four groups:

What are the kidney manifestations in patients with Waldenström Macroglobulinemia?

CJASN Clinical Journal of American Society of Nephrology

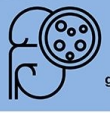
Cohort

57 kidney biopsies in patients with



Waldenström macroglobulinemia and other IgM secreting B-cell lymphoproliferative disorders

Outcomes



83% Monoclonal gammopathy related kidney lesions

18% Non-monoclonal gammopathy related kidney lesions

	Amyloid Glomerulopathy n=19	Non-Amyloid Glomerulopathy n=20	Tubulointerstitial lesions n=8	Non-monoclonal gammopathy n=10
Waldenström macroglobulinemia n=42	17	9	7	9
Monoclonal gammopathy of renal significance n=9	2	6	0	1
Other n=6	0	5	1	0

Conclusions This study demonstrates a diverse variety of kidney lesions in patients with monoclonal IgM gammopathy.

Larissa Higgins, Samih Nasr, Samar Said, et al. Kidney Involvement of Patients with Waldenström Macroglobulinemia and other IgM Producing B-Cell Lymphoproliferative Disorders. doi: 10.2215/CJN13041117

Da: Higgins L et al. Clin J Am Soc Nephrol 13: 1037–1046, July, 2018

Table 1. Kidney lesions of patients with Waldenström macroglobulinemia and other IgM monoclonal gammopathy

Group 1: Amyloid Glomerulopathy, *N*=19	Group 2: Nonamyloid Glomerulopathy, *N*=20	Group 3: Tubulointerstitial Lesions, *N*=8	Group 4: Nonparaprotein-Related Lesions, *N*=10
Monoclonal light-chain amyloidosis (16)	Cryoglobulinemic GN (12)	Lymphoma infiltration (4)	Minimal change disease (2)
Monoclonal light- and heavy-chain amyloidosis (2)	Immunotactoid GN (2)	Light-chain cast nephropathy (2)	Acute tubular necrosis (2)
Monoclonal light- and heavy-chain amyloidosis with membranous nephropathy (1)[a]	Intracapillary monoclonal deposits disease (2)	Lymphoma infiltration with light-chain cast nephropathy (1)[a]	Secondary FSGS (1)
	Proliferative GN with monoclonal Ig deposits (1)	Lymphoma infiltration and ANCA-associated GN (1)[a]	FSGS (1)
	Monoclonal IgG–associated membranous nephropathy (1)		Acute tubular necrosis and acute interstitial nephritis (1)
	Light-chain deposition disease (1)		Diabetic nephropathy (1)
	Mesangial proliferative GN with minimal change disease and lymphoma infiltration (1)[a]		Immune complex–mediated proliferative GN (1)
			Thrombotic microangiopathy (1)

[a]More than one pathologic feature.

Da: Uppal NN et al . Nephrol Dial Transplant (2018) 1–9

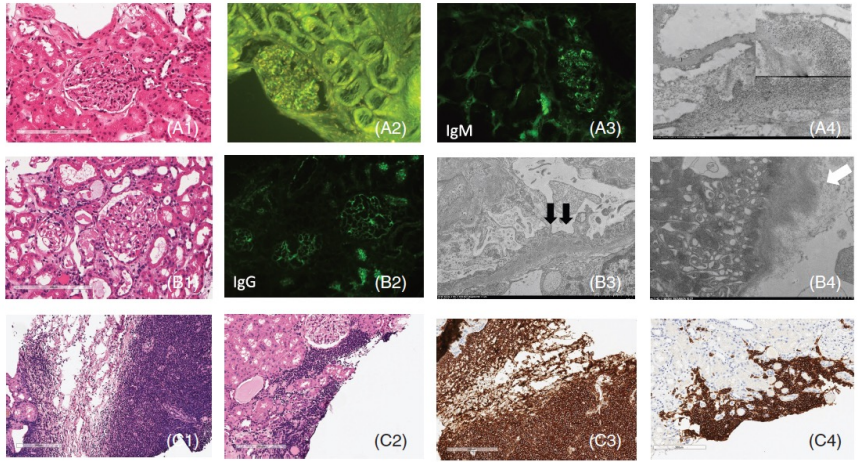
Received: 23 October 2023 | Revised: 29 February 2024 | Accepted: 9 March 2024
DOI: 10.1002/cnr2.2062

CASE SERIES

Cancer Reports WILEY

When Waldenström macroglobulinemia hits the kidney: Description of a case series and management of a “rare in rare” scenario

Nicolò Danesin[1] | Greta Scapinello[1] | Dorella Del Prete[2] | Elena Naso[2] | Tamara Berno[1] | Andrea Visentin[1] | Laura Bonaldi[3] | Annalisa Martines[3] | Roberta Bertorelle[3] | Fabrizio Vianello[1,4] | Carmela Gurrieri[1] | Renato Zambello[1,4] | Chiara Castellani[5] | Marny Fedrigo[5] | Stefania Rizzo[5] | Annalisa Angelini[5] | Livio Trentin[1] | Francesco Piazza[1,4]



Casistica Ematologia Padova (2000-2025, n=11)

- Amiloidosi 4 (36.4%)
- Glomerulopatia 5 (45.4%)
- Tubulo-interstiziopatia 2 (18.1%)

Danesin N. et al. Cancer Rep. 2024

Renal involvement in LPL/WM: treatments and outcomes

	Chauvet S n=35	Vos J n= 44	Higgins n= 57
Alkylating	70%	29%	na
Rituximab	22.7%	85%	58%
Purine analogues	8%	6%	na
Proteasome Inhibitors	0%	50%	na
Others (including ASCT)	1%	2%	16%
ORR hem	33%-99%	64%	42.3%
ORR Ren	50%-62.5%	73%	42.3%

Vos JM et al BJH 2016
Higgins L et al. Clin J Am Soc Nephrol 13: 1037–1046, July, 2018

Main recent prospective clinical trials in testing efficacy of Bortezomib-based regimens, such as ECWM-1 (B-DRC vs DRC), EMN (BDR) or BTKi-based regimens (ASPEN, INNOVATE) generally have considered the presence of renal dysfunction as an exclusion criterion (ClCr < 30 ml/min/1,73mq).

Trial	Phase	Arms	Elegibility	«Renal» exclusion criteria	Number of patients	Findings
ECWM-1 (JCO 2023)	3	B-DRC vs DRC	TN	Serum creatinine > 2 mg/dL	204	Higher CR/VGPR rate for B-DRC
EMN (Blood 2013)	2	BDR	TN	ClCt < 30 ml/min…	59	Long lasting response in TN patients
INNOVATE (NEJM, 2018)	3	Ibrutinib-Rituximab vs Rituximab	R/R or TN	Biochemical values within protocol limits…	150	Higher PFS rate for Ibrutinib-Rituximab
ASPEN (Blood, 2020)	3	Zanubrutinib vs Ibrutinib	R/R after a prior line or TN unsuitable for CHT	Inadequate renal function…	201	Higher CR/VGPR rate for Zanubrutinib

C Buske et al, J Clin Onc 2023; MA Dimopoulos, Blood 2013; MA Dimopoulos, NEJM 2018; CS Tam Blood 2020

Long title: Renal Dysfunction in Symptomatic Waldenström Macroglobulinemia: a Nationwide Italian Multicenter Study.

Authors: Nicolò Danesin[1], Francesco Autore[2], Anna Maria Frustaci[3], Gianmarco Favrin[18], Emanuele Cencini[5], Alessandro Noto[6], Irene Dogliotti[19], Jacopo Olivieri[7], Marcello Riva[8], Isacco Ferrarini[9], Anna Maria Barbui[10], Sara Steffanoni[11], Dario Marino[12], Benedetta Puccini[13], Piero Maria Stefani[14], Rita Rizzi[15], Michele Merli[6], Angela Ferrari[16], Stefano Luminari[16], Carlo Visco[9], Livio Trentin[1], Andrea Visentin[1], Annarita Conconi[17], Simone Ferrero[4,19], Marzia Varettoni[18], Alessandra Tedeschi[3], Luca Laurenti[2], Francesco Piazza[1].

Median FU 95.4 mo

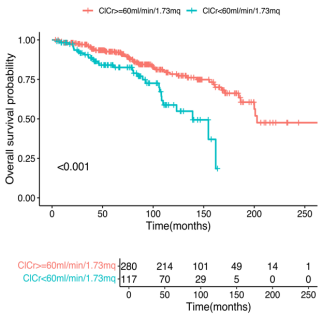
N=471 sWM; 402 study population

119/402 (29.6%) with eGFR < 60mL/min/1.73m2

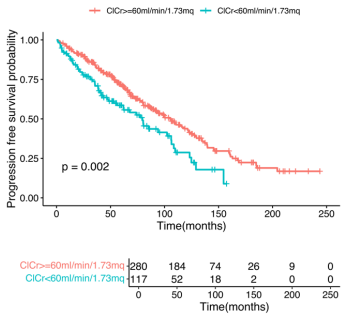
33/119 (27.7%) renal biopsied

WHOLE COHORT

mOS 139 vs 203 mo

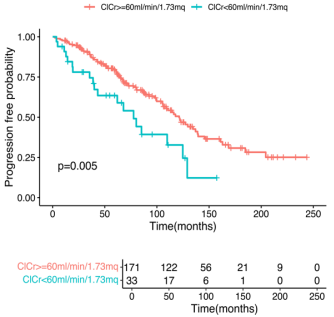


mPFS 80 vs 106 mo

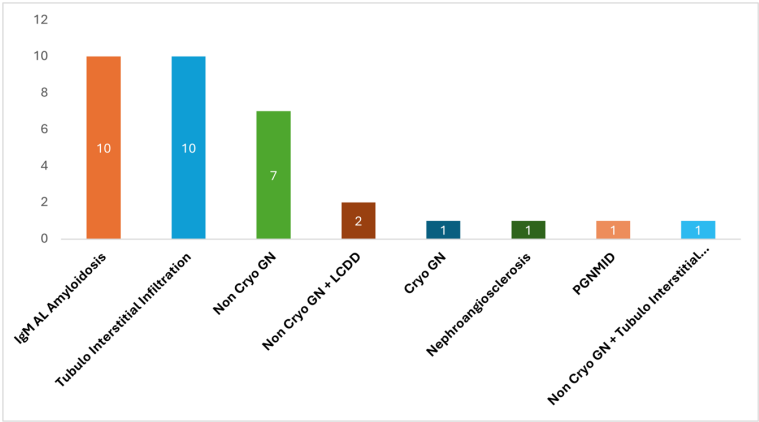


AGED < 70 YEARS

mPFS 77 vs 121 mo



Distribution of renal histopathological patterns in biopsied sWM patients (n = 33, 27.7% of those with renal impairment)



NA-GN 33.4%
A-GN 30.3%
Tubulointerstitial 30.3%
Other

Danesin N et al. Submitted BJH Major Revision

IgM/WM-related Kidney Lesions

a) May be **underestimated**.
b) The **prevailing** renal **lesions** are **glomerular**, both amyloidotic and non amyloidotic.
c) A correct **diagnostic work up** should be refined.
d) The **prognostic stratification** is unclear.
e) The most appropriate **therapeutic approach** is still debated.

Renal Impairment in WM

a) It should be assessed as a **possible expression of MGRS**/WMKD >>> biopsy.
b) It **impacts survival outcomes** in young and elderly patients.
c) It **responds well to CIT**, not enough data on novel modern treatments.

Acknowledgements

University of Padua - Department of Medicine
Padua University Hospital - Hematology
Head: Prof. Livio Trentin

Lymphoma Physicians
Dott.ssa Greta Scapinello
Dott. Nicolò Danesin (Resident)
Dott. Marco Carraro (Resident)

Nephrologists
Dott.ssa E. Naso
Dott.ssa D. De Giorgi
Prof.ssa D. Del Prete

Nephropathologists
Prof.ssa F. Angelini
Dott.ssa M. Fedrigo

Hematopathologist
Prof. Marco Pizzi

Thank You for Your Attention!