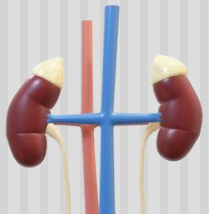
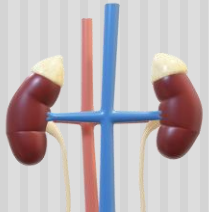
THE EVALUATION AND MANAGEMENT OF MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

- In 2012, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) formally defined MGRS as hematological clonal disorders that produce a monoclonal paraprotein associated with renal damage.
- In 2017, the IKMG updated the definition of MGRS to include any hematological condition, not only a malignancy, associated with a nephrotoxic monoclonal paraprotein causing renal injury. Therefore, the current diagnosis of MGRS does not require the presence of defined lymphoma or myeloma.



- (MGUS) is a benign condition with malignant potential.
- Based on the associated paraprotein, MGUS can be separated into two distinct groups,
- Non IgM MGUS, including IgG, IgA, and kappa or lambda free light chain (FLC) MGUS
- IgM MGUS.
- Upon progression, most individuals with non-IgM MGUS tend to develop multiple myeloma (MM) or systemic light chain (AL) amyloidosis, while most individuals with IgM MGUS progress into WM or other lymphoproliferative disorders.



- Despite its benign nature, MGUS can associate with organ dysfunction.
- Monoclonal gammopathy of renal significance (MGRS) and neurological significance (MGNS) can induce different degrees of morbidity and potential disability. Clinical experience suggests that patients with MGRS and MGNS could benefit from treatments used for hematologic malignancies.
- The treatment of MGRS and MGNS, however, is not standardized, and effective therapies might not be offered or reimbursed because these conditions do not meet the criteria for malignancy

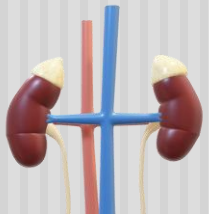


Table 3 | **Renal lesions associated with monoclonal gammopathy**

Lesion	Proportion of lesions (%)					
	Monoclonal immuno-globulin deposits	Detectable monoclonal immuno-globulin	MM	MGRS	Other[a]	Refs
Light-chain cast nephropathy	100	100	99	0	~1	2,4,11,13
Immunoglobulin-related amyloid amyloidosis	96	99	16	80	1–4	43,113,128,129
MIDD	100	100	0–20	78–100	1–2	29,31,68,130,131
Light-chain proximal tubulopathy	100	97[b]	12–33	61–80	3–8	32,56,58,132
Cryoglobulinaemic (type I) glomerulonephritis	100	90–100	6–8	47–52	24–56	133–136
Cryoglobulinaemic (type II) glomerulonephritis	100	49	0	20	7	133–136
PGNMID	100	30–32	4	96	~1	24,72
Crystal-storing histiocytosis	83	90	33	8	50	137
Cryocrystalglobulin or crystalglobulin nephropathy	91	82	61	18	4	138
Immunotactoid glomerulonephritis	69–93	63–71	0–13	25–50	25–50	23,51
C3 glomerulopathy with monoclonal gammopathy[c]	0	28–83[d]	0–40[d]	40–90	6–10	25,74,75,104
Monoclonal fibrillary glomerulonephritis[e]	100	7–17	0–54	55–98	2–10	44,47,139

MGRS, monoclonal gammopathy of renal significance; MIDD, monoclonal immunoglobulin deposition disease; MM, multiple myeloma; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits. [a]Haematological conditions including lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia), smouldering Waldenström macroglobulinaemia, B cell lymphomas, chronic lymphocytic lymphoma and monoclonal B cell lymphocytosis. [b]Sensitivity increased by immunofluorescence after pronase digestion. [c]Most instances of fibrillary glomerulonephritis and C3 glomerulopathy are not associated with a monoclonal gammopathy. The percentages for MM, MGRS and other haematological conditions relate to the group of patients who do have a monoclonal gammopathy. [d]Patients over the age of 50 years. [e]In these patients, the glomerular deposits show light-chain restriction or stain for IgG without light chains, both by frozen tissue and paraffin tissue immunofluorescence (as in 15–17% of patients with fibrillary glomerulonephritis).

Table 1 | **Characteristics of clonal B cell and plasma cell proliferative disorders**

Disease	Clone	Bone marrow involvement	Immunoglobulin	M-spike	Organ damage and/or involvement
MGUS	Any	<10%	Any	<30 g/l	None
Smouldering MM[a]	Plasma cell	10–60%	Any	≥30 g/l	None
MM[a]	Plasma cell	≥10%	Any	≥30 g/l	SLiM CRAB: 60% bone marrow plasma cells, involved:uninvolved free light-chain ratio >100, >1 bone lesion on MRI, hypercalcaemia, renal impairment, anaemia and lytic bone lesions
Smouldering WM[a]	Lymphoplasmacytic lymphoma clone[b]	≥10%	IgM	≥30 g/l	Absent
WM[a]	Lymphoplasmacytic lymphoma clone[b]	≥10%	IgM	≥30 g/l	Anaemia, hyperviscosity, constitutional symptoms, bulky lymphadenopathy, hepatosplenomegaly and neuropathy
MBL	B-cell clone[c]	Peripheral B-cell count $<5 \times 10^9$/l	Any	Any	Absence of lymph node involvement
CLL	B-cell clone[c]	Peripheral B-cell count $>5 \times 10^9$/l	Any	Any	Adenopathy, anaemia and thrombocytopenia
Other B cell lympho-proliferative disorders	Pan B-cell markers ($CD19^+CD20^+CD79^+CD22^+PAX5^+$)	Presence or absence	Any	Any	Adenopathy and splenomegaly

CLL, chronic lymphocytic leukaemia; MBL, monoclonal B cell lymphocytosis; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SLiM CRAB, symptomatic, light chains, MRI, high calcium, renal dysfunction, anaemia, and bony lytic lesions; WM, Waldenström macroglobulinaemia. [a]Either bone marrow involvement or an M-spike above these thresholds is sufficient for the diagnosis. [b]Typically, B cells are surface $IgM^+CD5^-CD10^-CD11c^-CD19^+CD20^+CD22^+CD23^-CD25^+CD27^+FMC7^+CD103^-CD138^-$ with a plasmacytic component that is $CD138^+CD38^+CD19^+CD45^+CD56^-$. [c]$CD5^+CD19^+CD23^+$surface immunoglobulin$^+CD20^{dim}$.

Table 1

Monoclonal gammopathy of renal significance – monoclonal gammopathy of clinical significance.

Pure MGRS	MGCS with frequent renal involvement	MCGS with rare renal involvement
PGNMID Immuno-tactoid nephropathy C3 glomerulopathy Light chain proximal tubulopathy	AL(H) amyloidosis MIDD Cryoglobulinemia type 1 and 2 Thrombotic microangiopathy Crystal-storing histiocytosis	POEMS Monoclonal gammopathy of cutaneous/neurologic/other significance

MIDD monoclonal immunoglobulin deposition disease - PGNMID proliferative glomerulonephritis with monoclonal immunoglobulin deposits – POEMS poly-neuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities.

Table 2

Classification of MGRS-associated renal diseases based on types of deposits.

MIg deposits	Non-organized	PGNMID	
		MIDD	
	Organized	Fibrillar	AL (H) amyloidosis
			Fibrillary GN
		Microtubular	Immunotactoid GN
			Cryoglobulinemic GN
		Crystalline	LCPT
			CSH
			Crystalglobulin GN
No MIg deposits	C3 glomerulopathy		
	Thrombotic microangiopathy		

Table 3

Classification of MGRS-associated renal diseases based on the main compartment affected.

Types of Deposits	Glomerular Compartment	Tubulointerstitial Compartment	Vascular Compartment
Organized Deposits	AL(H) amyloidosis	LCPT	
	Fibrillary GN	CSH	
	Immunotactoid GN	Crystalglobulin GN	
	Cryoglobulinemic GN	AL(H) amyloidosis	
Non Organized Deposits	PGNMID	MIDD	
	MIDD		
No Deposits	C3GN		C3GN
	TMA		TMA

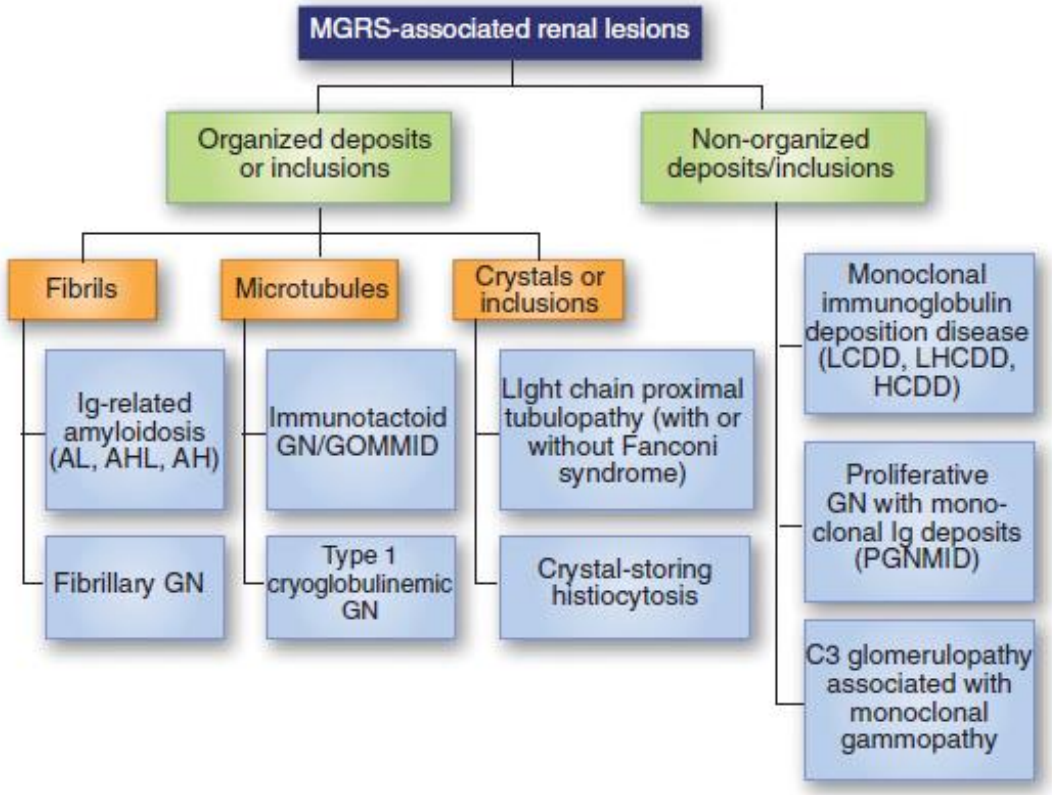
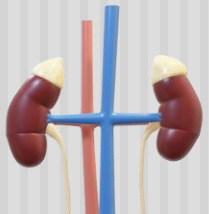
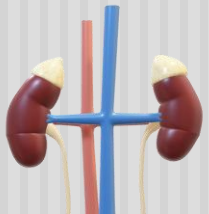


Figure 2 | Diagram of MGRS-associated renal lesions.
AH, immunoglobulin heavy chain amyloidosis; AHL, immunoglobulin heavy and light chain amyloidosis; AL, immunoglobulin light chain amyloidosis; GN, glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits; HCDD, heavy chain deposition disease; LCDD, light chain deposition disease; LHCDD, light and heavy chain deposition disease; MGRS, monoclonal gammopathy of renal significance; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin G deposits.

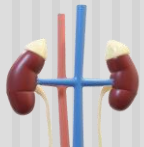
- The diagnosis of MGRS can only be established with **renal biopsy.** The classification of MGRS-associated renal lesions proposed by the IKMG in 2017 is based on light microscopy, immunofluorescence studies, and electron microscopy (EM) findings on material obtained from such biopsies. Light microscopy and immunofluorescence are mandatory for proper evaluation of MGRS. Note, EM evaluation is encouraged but not required, given accessibility limitations. The findings of light chain cast nephropathy, or monoclonal plasma cell infiltration in the kidney biopsy, represent multiple myeloma diagnoses and must be managed accordingly.



- A kidney biopsy is at the center of the evaluation of MGRS. However, it is essential to evaluate patients for other causes of kidney dysfunction. A study showed that about half of the patients with concurrent MGUS and chronic kidney dysfunction did not have MGRS lesions on kidney biopsy. The risk of under diagnosis should be balanced against the risk of the procedure itself, especially in frail patients in whom treatment might not be pursued. Renal biopsies have been associated with a small risk of bleeding. A transjugular kidney biopsy is an option in patients at high risk for complications from transcutaneous biopsy.



- The diagnosis of MGRS is established by kidney biopsy, as well as the patient's medical history, bone marrow biopsy, imaging, and laboratory data.
- For confirmation of monoclonal immunoglobulin deposits, immunofluorescence staining for IgG subclasses, IgA and IgM, as well as light chains, is recommended.
- Positive staining for C1q or C3 proteins can be seen in patients with MGRS lesions such as PGNMID, immunotactoid glomerulonephritis, type I cryoglobulinemic glomerulonephritis, C3 glomerulonephritis, and monoclonal immunoglobulin deposition disease (MIDD). Pronase digestion might be used for unmasking immunoglobulins in paraffin-fixed samples.



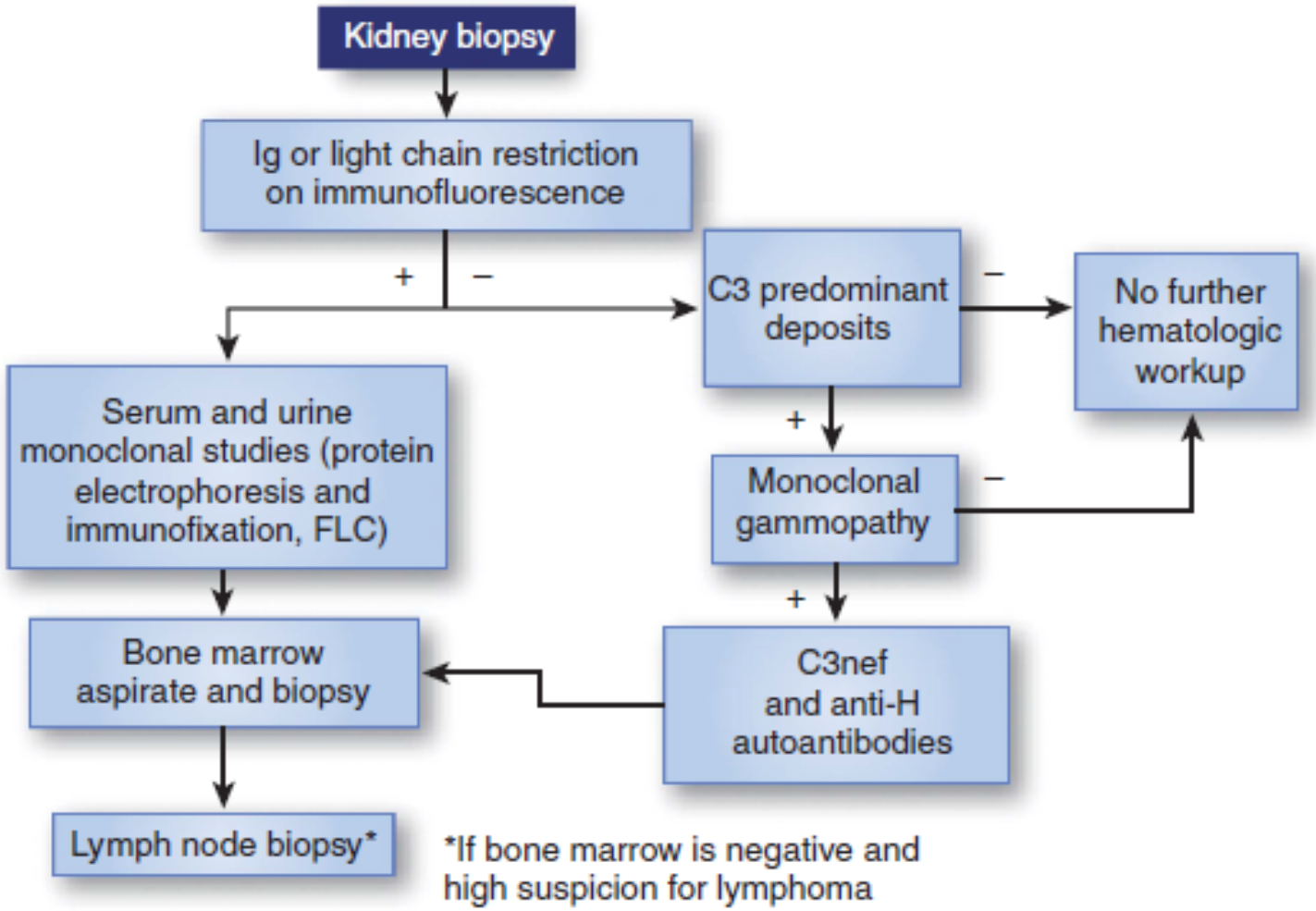
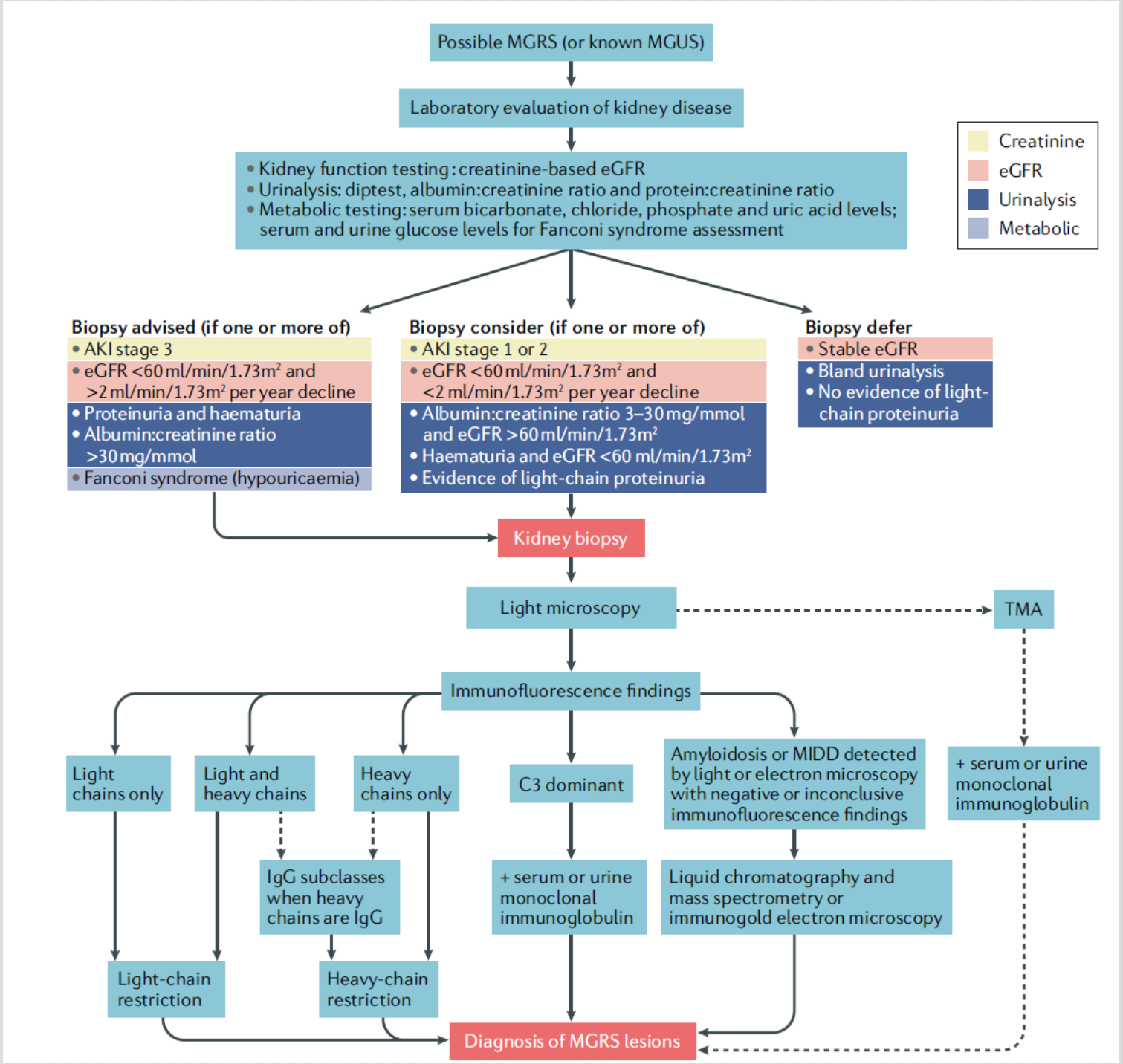


Figure 1 | Proposed algorithm for hematologic workup in patients with MGRS. MGRS, monoclonal gammopathy of renal significance; FLC, serum-free light chain assay.


Possible MGRS (or known MGUS)
Laboratory evaluation of kidney disease
• Kidney function testing: creatinine-based eGFR
• Urinalysis: diptest, albumin:creatinine ratio and protein:creatinine ratio
• Metabolic testing: serum bicarbonate, chloride, phosphate and uric acid levels; serum and urine glucose levels for Fanconi syndrome assessment
Creatinine
eGFR
Urinalysis
Metabolic
Biopsy advised (if one or more of)
• AKI stage 3
• eGFR <60 ml/min/1.73m² and >2 ml/min/1.73m² per year decline
• Proteinuria and haematuria
• Albumin:creatinine ratio >30 mg/mmol
• Fanconi syndrome (hypouricaemia)
Biopsy consider (if one or more of)
• AKI stage 1 or 2
• eGFR <60 ml/min/1.73m² and <2 ml/min/1.73m² per year decline
• Albumin:creatinine ratio 3–30 mg/mmol and eGFR >60 ml/min/1.73m²
• Haematuria and eGFR <60 ml/min/1.73m²
• Evidence of light-chain proteinuria
Biopsy defer
• Stable eGFR
• Bland urinalysis
• No evidence of light-chain proteinuria
Kidney biopsy
Light microscopy
TMA
Immunofluorescence findings
Light chains only
Light and heavy chains
Heavy chains only
C3 dominant
Amyloidosis or MIDD detected by light or electron microscopy with negative or inconclusive immunofluorescence findings
+ serum or urine monoclonal immunoglobulin
IgG subclasses when heavy chains are IgG
+ serum or urine monoclonal immunoglobulin
Liquid chromatography and mass spectrometry or immunogold electron microscopy
Light-chain restriction
Heavy-chain restriction
Diagnosis of MGRS lesions

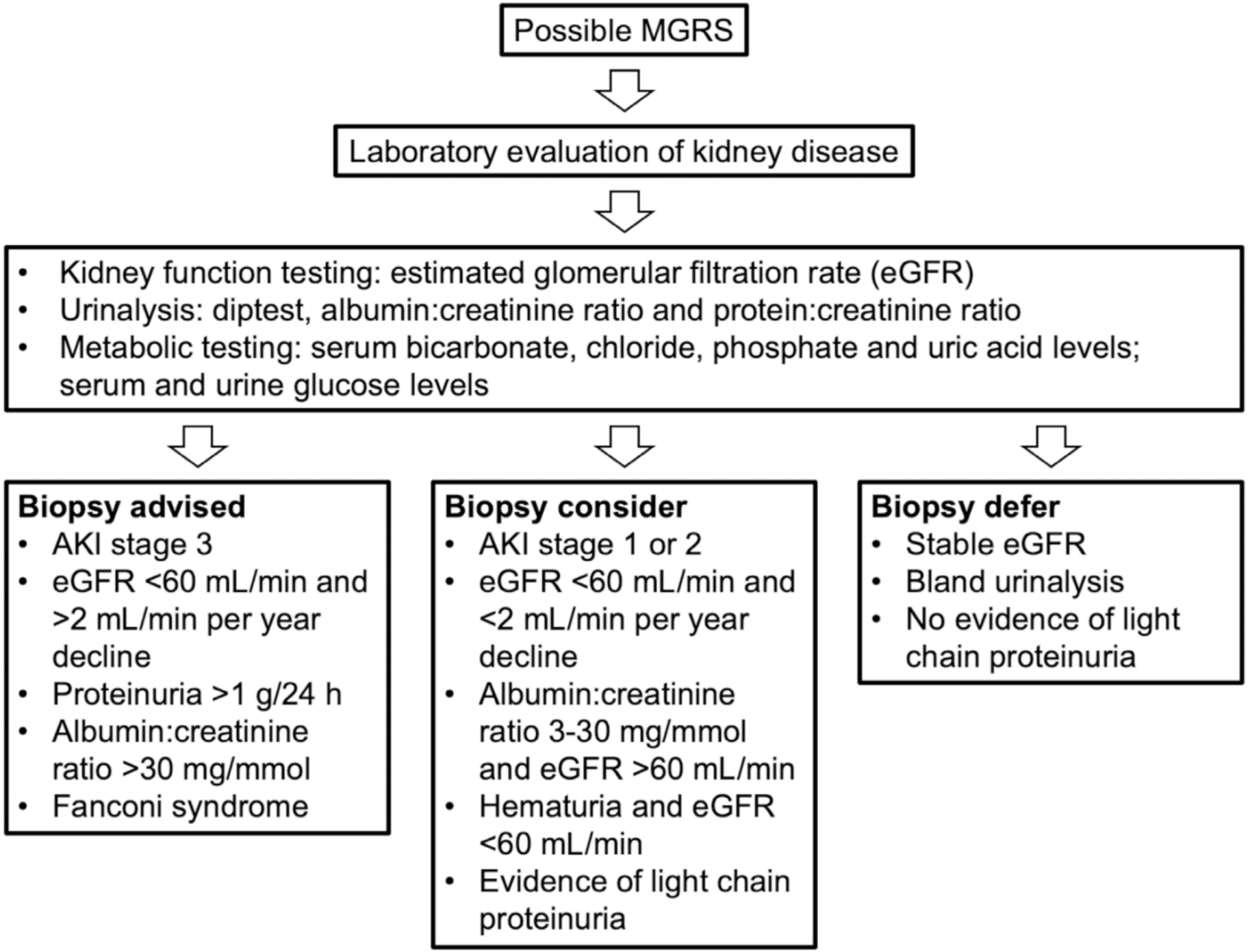


FIGURE 1 Proposed algorithm for renal biopsy in patients with monoclonal gammopathy of renal significance. Adapted from.[4] AKI, acute kidney injury; MGRS, monoclonal gammopathy of renal significance

Table 4

Renal symptoms.

MGRS-associated renal disease	Renal symptoms
Fibrillary and immunotactoid GN	(nephrotic-range) proteinuria, hematuria, progressive renal insufficiency
AL(H) amyloidosis	Nephrotic syndrome, renal insufficiency
Cryoglobulinemic GN	Hematuria, nephrotic syndrome, progressive renal insufficiency, hypertension
Light chain proximal tubulopathy	Fanconi syndrome
MIDD	proteinuria, nephrotic syndrome, renal insufficiency
PGNMID	Proteinuria, hematuria, hypertension, renal insufficiency

TABLE 1 Classification of monoclonal gammopathy of renal significance-associated renal lesions

Monoclonal immunoglobulin deposits				
Organized				
Fibrillar	**Microtubular**	**Inclusions or crystalline deposits**	**Non-organized**	**No monoclonal immunoglobulin deposits**
AL amyloidosis • Congo red positive • Fibril diameter: 7–12 nm Monoclonal fibrillary glomerulonephritis • Congo red negative • Fibril diameter: 10–30 nm	Immunotactoid glomerulonephritis • Diameter: 17–52 nm, hollow • Parallel distribution Cryoglobulinemic glomerulonephritis • Diameter: 17–52 nm, hollow • Not organized	Light chain proximal tubulopathy • Crystalline variant: *kappa*, Fanconi syndrome common • Non-crystalline variant: *lambda*, Fanconi syndrome rare Crystal storing histiocytosis • Renal histiocytes • BM, LN, lungs Crystal globulin glomerulonephritis • Ig thrombi in glomerular capillaries	Monoclonal immunoglobulin deposition disease • Light or heavy chains distributed along GBM and TBM • IgG1 Proliferative glomerulonephritis and monoclonal immunoglobulin deposition • Glomerular deposition • IgG3, IgA, IgM (rare)	C3 glomerulopathy with monoclonal gammopathy • Monoclonal gammopathy detectable in 60–80% of individuals >50 years with C3 glomerulonephritis Thrombotic microangiopathy • Provisional POEMS • Provisional

Note: Adapted from[4].

Abbreviations: BM, bone marrow; GBM, glomerular base membrane; LN, lymph node; TBM, tubular base membrane.

Table 2 | **Consensus recommendations for the evaluation of MGRS-associated disorders**

Modality	Recommendations	Refs
Kidney biopsy	Recommended in the following patients: • Those with monoclonal gammopathy and unexplained kidney disease • Those with known risk factors for chronic kidney disease but an atypical clinical course • Patients with kidney disease and monoclonal gammopathy aged <50 years	NA
Protease immunofluorescence on kidney biopsy	Recommended in the following scenarios: • When glomeruli are lacking in frozen tissue samples • In patients with suspected LCPT and other forms of crystalline nephropathies, such as CSH and crystalglobulin-induced nephropathy • In patients with a monoclonal gammopathy in whom kidney biopsy samples show C3 glomerulonephritis or unclassified proliferative glomerulonephritis in the context of negative findings by immunofluorescence on frozen tissue samples (including in patients with features of cryoglobulinaemic glomerulonephritis on light or electron microscopy) • In patients with fibrillary glomerulonephritis who have apparent light-chain restriction detected by immunofluorescence on frozen tissue	NA
Renal amyloid typing by liquid chromatography and mass spectrometry	Recommended in the following situations: • When frozen tissue for immunofluorescence is not available • Negative immunofluorescence staining for κ and λ light chains, with negative immunoperoxidase staining for SAA and LECT2 • Equal staining for κ and λ light chains by immunofluorescence • Bright staining for IgG and/or IgA by immunofluorescence • Equivocal Congo red staining • To enable distinction between AHL amyloidosis and congophilic fibrillary glomerulonephritis	108
Flow cytometry or other immunotyping	• Neoplastic plasma cells frequently show aberrant loss of CD45 and CD19, as well as aberrant expression of CD56 and CD117; therefore, these markers (in addition to κ and λ light chains and CD38) are useful in identifying small plasma cell clones • Including CD5 and CD20 in the immunophenotyping of B cells can frequently separate small clones from polytypic cells • The most sensitive assay available at a given institution should be used. Although there is no established gold standard, many laboratories have the capability to determine minimal residual disease in MGRS at a sensitivity of 10^{-4} to 10^{-6} monoclonal cells. The sensitivity of flow cytometry immunophenotyping depends on the total number of collected cells, the number of antibodies used to find an aberrant phenotype, the phenotype of the abnormal clone and sample quality	118
Immunohistochemistry	• Immunohistochemistry of bone marrow biopsy samples has a low sensitivity for detecting κ-expressing and λ-expressing plasma cells and could be useful only if there is a major plasma cell clone and a lack of polyclonal plasma cells • Immunohistochemistry might be useful in the evaluation of atypical lymphoid infiltrates, particularly if flow cytometry is not available or infiltrates are very focal • If an abnormal clone is detected, the light-chain isotype should be compared with that present in renal lesions and additional information should be obtained	NA
Mutational analysis	The MYD88 L265P mutation is found in over 90% of patients with lymphoplasmacytic lymphoma or Waldenström macroglobulinaemia but in only 40–60% of individuals with IgM MGUS	119–121
FISH	Cyclin D1 FISH with immunostaining for CD10, BCL2 and BCL6 to subclassify diffuse large cell lymphoma, and prognostic FISH panels for MM and CLL, can also be useful	119–121

AHL, immunoglobulin A heavy-and-light chain; CLL, chronic lymphocytic leukaemia; CSH, crystal-storing histiocytosis; FISH, fluorescence in situ hybridization; LCPT, light-chain proximal tubulopathy; LECT2, leukocyte cell-derived chemotaxin 2; MGRS, monoclonal gammopathy of renal significance; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NA, not applicable; SAA, serum amyloid A protein.

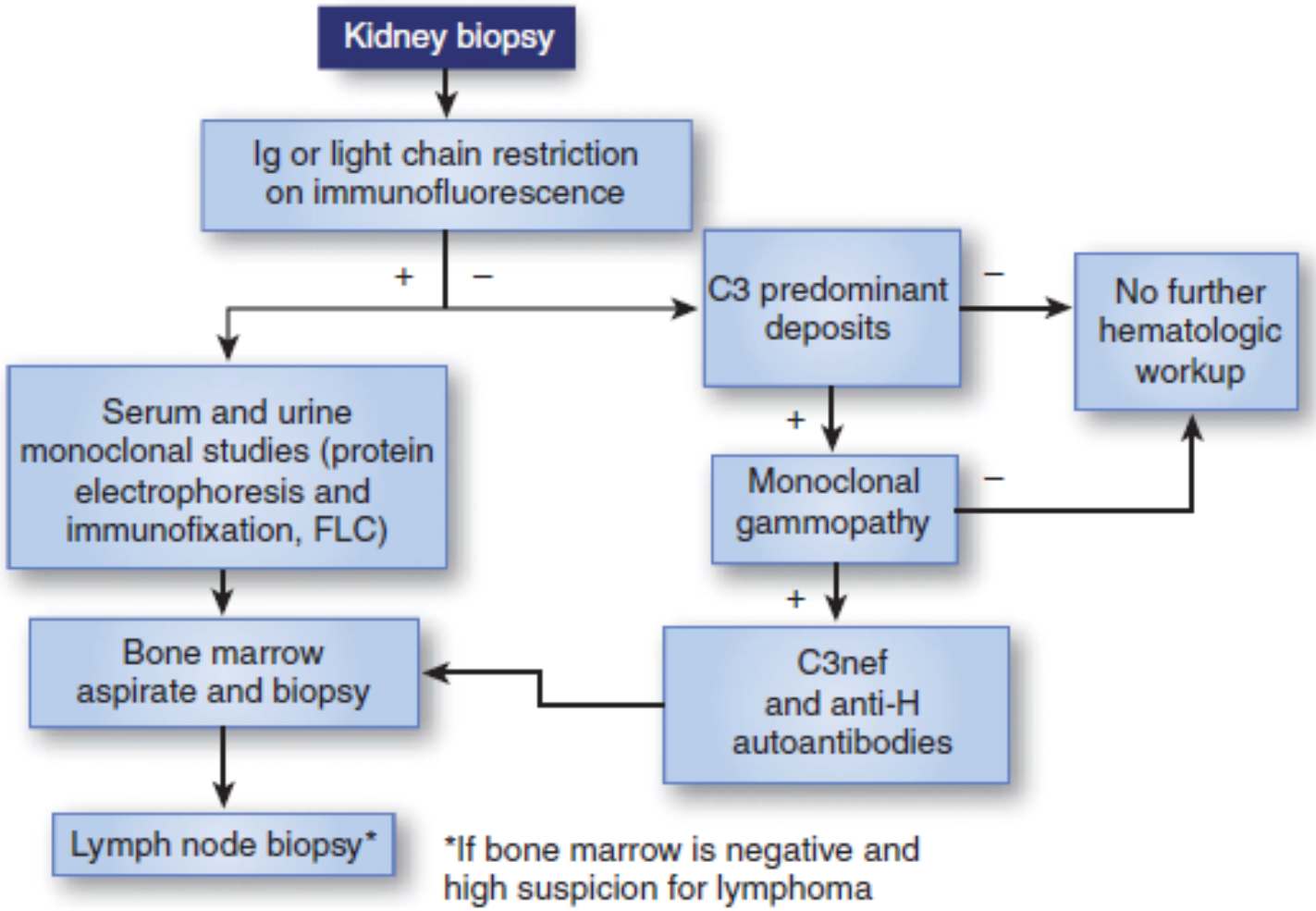


Figure 1 | Proposed algorithm for hematologic workup in patients with MGRS. MGRS, monoclonal gammopathy of renal significance; FLC, serum-free light chain assay.

Table 3 | Main clinical, pathological, and immunological characteristics of glomerular disorders with non-organized Ig deposits in MGRS

Glomerular disease	Renal symptoms	Light microscopic pattern	IF findings (Ig type)	Ultrastructural findings	Extrarenal involvement	Identification of an M-protein	Hematological and immunological characteristics
MIDD	Proteinuria, NS CKD Microhematuria Hypertension	Nodular glomerulosclerosis (constant in HCDD) Thickened TBM and vascular walls	Linear deposits along TBM, GBM and around arteriolar/arterial myocytes LCDD: mostly kappa (Vκ4) HCDD: truncated HC (γ1, or γ3, or γ4, or α), with CH1 deletion. C3 deposits in γ1 and γ3 HCDD LHCDD: LC + truncated HC deposits	Amorphous deposits in TBM, GBM, mesangium and arteriolar/arterial walls	Common, often asymptomatic: heart, liver, lung	Serum EP/immunofixation: 25–76% in LCDD, 80–100% in LHCDD, 67–100% in HCDD Urine EP/immunofixation: 42–90% in LCDD, 80–100% in LHCDD, 50–100% in HCDD FLC: 100% in LCDD, LHCDD, HCDD	MGRS Symptomatic MM WM[a] Hypocomp. common in γ1 and γ3 HCDD
PGNMID	Proteinuria, NS CKD Microhematuria Hypertension	MPGN Endocapillary GN Membranous GN Mesangial GN	Granular deposits in mesangium, CW Monotypic IgG deposits: IgG3 most common, or IgG1, or IgG2 (κ > λ) Rarley, monotypic IgM, IgA, or LC deposits C3 + C1q deposits	Non-organized granular deposits in mesangium, subendothelial and/or subepithelial zone	None	Serum EP/immunofixation: 30% Urine EP/immunofixation: 11% FLC: UN	Usually none MGRS MM, B-cell lymphoma, WM: rare Hypocomp. ~30%
C3 glomerulopathy with monoclonal gammopathy	Proteinuria, NS CKD Microhematuria Hypertension	MPGN Mesangial GN Endocapillary proliferative GN	Granular C3 deposits in mesangium and CW No or paucity of Ig deposits	'Sausage shaped' intramembranous and large rounded mesangial electron dense deposits in DDD Ill-defined mesangial, intramembranous and subendothelial electron dense deposits in C3GN Humps common in DDD and C3GN	None	Serum EP/immunofixation: 100% Urine EP: 100% FLC: 75–100%	MGRS MM Hypocomp. common, with low C3 and occasionally anti-complement factor H autoantibody

Abbreviations: CKD, chronic kidney disease; CW, glomerular capillary walls; DDD, dense deposit disease; EP, electrophoresis; FLC, serum-free light chain assay; GBM, glomerular basement membrane; GN, glomerulonephritis; C3GN, C3 glomerulonephritis; HCDD, heavy chain deposition disease; Hypocomp., hypocomplementemia; IF, immunofluorescence; Ig, immunoglobulin; LC, immunoglobulin light chains; LCDD, light chain deposition disease; LHCDD, light and heavy chain deposition disease; MGRS, monoclonal gammopathy of renal significance; MIDD, monoclonal immunoglobulin deposition disease (Randall-type); MM, multiple myeloma; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits; TBM, tubular basement membrane; UN, unknown; WM, Waldenstrom's macroglobulinemia.
[a]In patients with IgM monoclonal gammopathy.

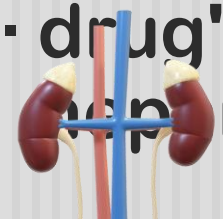
Table 2 | Main clinical, pathological, and immunological characteristics of glomerular disorders with organized Ig deposits in MGRS

Glomerular disease	Renal symptoms	Light microscopic findings	IF findings (Ig type)	Ultrastructural findings	Extra-renal involvement	Identification of an M-protein	Hematological and immunological characteristics
AL amyloidosis *AH amyloidosis* *AHL amyloidosis*	Proteinuria, NS CKD Hypertension and hematuria uncommon	Congo-red-positive mesangial and CW deposits (dichroism + birefringence under polarized light) Vascular and tubulo interstitial involvement common	AL: LC deposits, mostly lambda AH: HC deposits (γ1, or γ4, or α), with first constant domain (CH1) deletion AHL: LC and HC deposits, mostly $\gamma+\lambda$ or $\alpha+\kappa$	Randomly arranged unbranched fibrils 7–14 nm in diameter	Frequent: heart, liver, peripheral nerve	Serum EP/immunofixation: 66-80% in AL, 88% in AH/AHL -Urine EP/immunofixation: 67% in AL, 80% in AH/AHL -FLC: 76-88% in AL, 82% in AH/AHL	MGRS Symptomatic MM uncommon WM[a]
ITGN/GOMMID	Proteinuria, NS CKD Microhematuria Hypertension	Mesangial GN with membranous features MPGN Interstitial tumoral infiltrate common (CLL)	Granular/smudgy deposits in mesangium and CW (pred. subepithelial) Monotypic IgG deposits (IgG1 > IgG2 > IgG3) ($\kappa>\lambda$) C3, C4, C1q deposits	Parallely arranged microtubules 10-60 nm, with hollow core	Uncommon (peripheral nerve, skin)	Serum EP/immunofixation: 35-67% Urine EP/immunofixation: 21–53% -FLC: 20%	CLL (common) B-cell lymphoma MGRS MM uncommon Hypocomp. ~30%
Type I cryoglobulinemic GN	Proteinuria, NS CKD Microhematuria Hypertension Possible nephritic syndrome, AKI, anuria	MPGN Endocapillary GN Glomerular thrombi common Intrarenal vasculitis occasional	Granular deposits in mesangium, CW (pred. subendothelial), vascular walls Glomerular thrombi Monotypic IgG, IgM, or IgA ($\kappa>\lambda$) - C3, C4, C1q deposits	Microtubules 10 to 90 nm Extra + intracellular crystals (crystal-cryoglobulinemia)	Frequent: skin, peripheral nerve, joints	Serum EP/immunofixation: 76% Urine EP/immunofixation: UN FLC: UN	MGRS MM B-cell lymphoma WM[a] Hypocomp. common

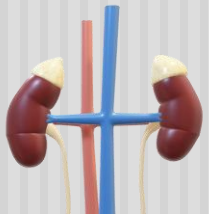
Abbreviations: AH, immunoglobulin heavy chain; AHL, immunoglobulin heavy and light chain; AL, immunoglobulin light chain; AKI, acute kidney injury; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; CW, glomerular capillary walls; EP, electrophoresis; FLC, serum-free light chain assay; GN, glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular immunoglobulin deposits; HC, immunoglobulin heavy chains; Hypocomp., hypocomplementemia; IF, immunofluorescence; Ig, immunoglobulin; ITGN, immunotactoid glomerulonephritis; LC, immunoglobulin light chains; MM, multiple myeloma; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; Pred., predominantly; UN, unknown; WM, Waldenström's macroglobulinemia.

[a]In patients with IgM monoclonal gammopathy.

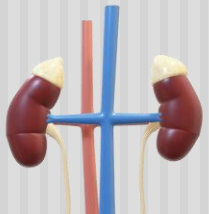
- Treatment recommendations were provided by the IKMG in 2012. Without active therapy against the B-cell clone producing the nephrotoxic monoclonal paraprotein, the natural course of MGRS is characterized by progressive renal dysfunction followed by end-stage renal disease (ESRD).
- The choice of therapy should take into account the
- patient's age,
- clinical presentation,
- comorbidities,
- genomic profiling
- preferences
- drug's renal metabolism and potential renal toxicity. Working with a nephrologist with experience is positively encouraged.



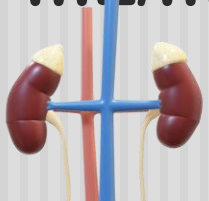
- Non-IgM and FLC-associated MGRS should be managed as per the treatment algorithm for MM unless another lymphoproliferative disorder is confirmed.
- Immunomodulating agents (e.g., thalidomide and pomalidomide) and proteasome inhibitors (e.g., bortezomib, carfilzomib, and ixazomib) can be used in MM patients with renal impairment without dose adjustments, while other drugs such as lenalidomide require dose modifications.



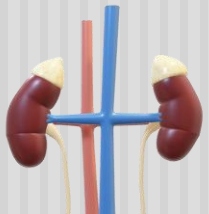
- The safety and efficacy of daratumumab and elotuzumab have been demonstrated in MM patients with renal dysfunction.
- High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) can be a treatment option in patients with MM renal impairment, including those with ESRD.
- In rare cases in which MGRS is accompanied by a solitary plasmacytoma, local radiation therapy can achieve control of the renal damaging paraprotein.



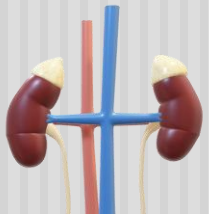
- IgM-associated MGRS should follow the treatment algorithm for WM. Cyclophosphamide and bendamustine are preferred over melphalan or fludarabine, given melphalan toxicity in patients with reduced renal function and fludarabine-associated renal metabolism as well as the stem cell toxicity associated with these agents.
- Bendamustine can be safely used at reduced doses in patients with abnormal renal function.
- Proteasome inhibitors and rituximab can be safely used in the setting of renal dysfunction without dose adjustments.
- The Bruton tyrosine kinase (BTK) inhibitor ibrutinib can be used in patients with an estimated glomerular filtration rate (GFR) >25 mL/min.



- In MGRS cases with underlying features consistent with monoclonal B-lymphocytosis, treatments for chronic lymphocytic leukemia (CLL) should be considered.
- Bendamustine, cyclophosphamide, rituximab, and ibrutinib can be safely administered in patients with renal dysfunction. Similar to rituximab, ofatumumab and obinutuzumab can be safely administered in patients with renal impairment. Venetoclax does not need dose adjustments in patients with estimated GFR >30 mL/min



- with estimated GFR >30 mL/min.The hematological response should be assessed using the response criteria for MM in non-IgM and criteria for WM in IgMassociated MGRS. In MGRS cases in which the causal monoclonal paraprotein is challenging to measure, the response should be assessed using renal function, resolution or improvement in proteinuria, bone marrow involvement, or radiological findings. More sensitive approaches for the detection of monoclonal protein, such as mass spectrometry, may be useful in patients where traditional immunofixation approaches do not detect a monoclonal protein



- The goal of therapy should focus on preventing further renal damage by the monoclonal paraprotein and allowing for recovery of such damage. Therefore, pursuing a deep response characterized by hematological response and disappearance of the serum monoclonal gammopathy and normalization of FLC ratio is reasonable.Evidence of relapse of the nephrotoxic monoclonal paraprotein should prompt reinitiation of therapy based on treatment algorithms for MM, WM, AL amyloidosis, or CLL. Treatment at relapse should be tailored, considering the response to and toxicity of prior therapy, patient's performance status, and renal function at the time of relapse.

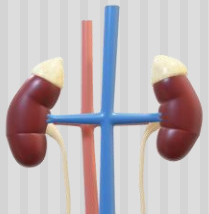


TABLE 2 Tests to consider for evaluation of monoclonal gammopathy of neurological significance

Laboratory tests	Radiological tests	Pathological tests	Neurological tests
Complete blood count	CT scan of the chest, abdomen and pelvis with IV contrast	Bone marrow biopsy	Nerve conduction studies
Comprehensive metabolic panel	PET/CT scan	MYD88 mutation analysis	Electromyography
SPEP with immunofixation	Skeletal survey	CSF cytology and flow cytometry	
Serum immunoglobulin levels	Whole-body MRI	Fat pad biopsy	
Serum free light chain levels	Brain and spine MRI with gadolinium	Nerve biopsy	
Cryoglobulins			
Anti-MAG antibodies			
Anti-ganglioside antibodies			
Hemoglobin A1c, fasting glucose or OGTT			
Serum cobalamin level			
Serum TSH level			
HIV antibody testing			
Lyme antibody testing			
Syphilis testing			
ANA titer			
Serum troponin levels			
Serum NT-proBNP levels			
VEGF level			

Abbreviations: ANA, antinuclear antibody; BNP, brain natriuretic peptide; CSF, cerebrospinal fluid; CT, computerized tomography; MAG, myelin-associated glycoprotein; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PET, positron emission tomography; SPEP, serum protein electrophoresis; TSH, thyroid stimulating hormone; VEGF, vascular endothelial growth factor.

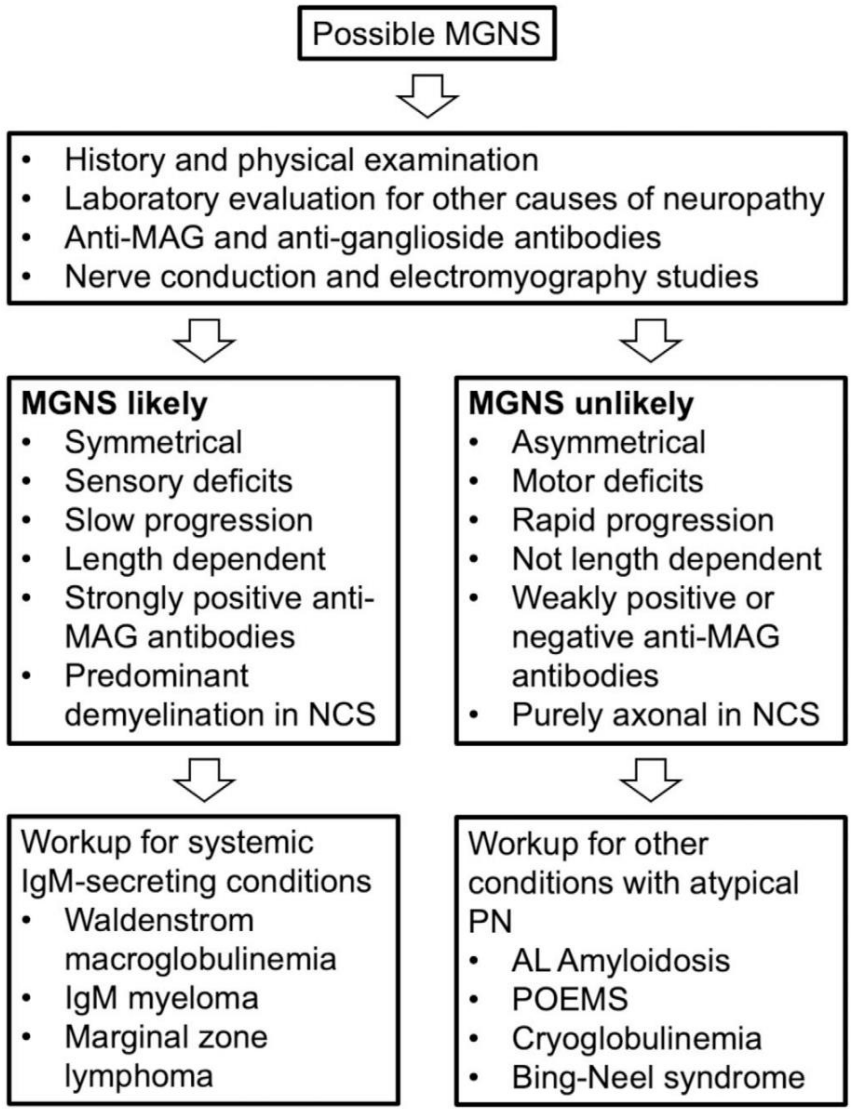


FIGURE 2 Proposed algorithm for evaluation of patients with monoclonal gammopathy of neurological significance. Adapted from.[34] MAG, myelin-associated glycoprotein; MGNS, monoclonal gammopathy of neurological significance; NCS, nerve conduction studies; PN, peripheral neuropathy; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes