MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE [MGRS]

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INTRODUCTION

- Kidney and Monoclonal Gammopathy Research Group in 2019 defined **MGRS** as any clonal B-cell or plasma cell lymphoproliferative disorder which fulfils both of the following **criteria** : -

1.Kidney lesions on biopsy that are related to the produced monoclonal immunoglobulin (the nephrotoxic MIg) and

2.The underlying haematological condition does not cause tumour complications or meet any of the current haematological indications for specific therapy.

- The **predictors** of finding an MGRS lesion :-
  1. elevated serum free light chain (SFLC) ratio,
  2. significant proteinuria (>1.5 g/d) and
  3. microscopic hematuria.

CLINICAL CLUES

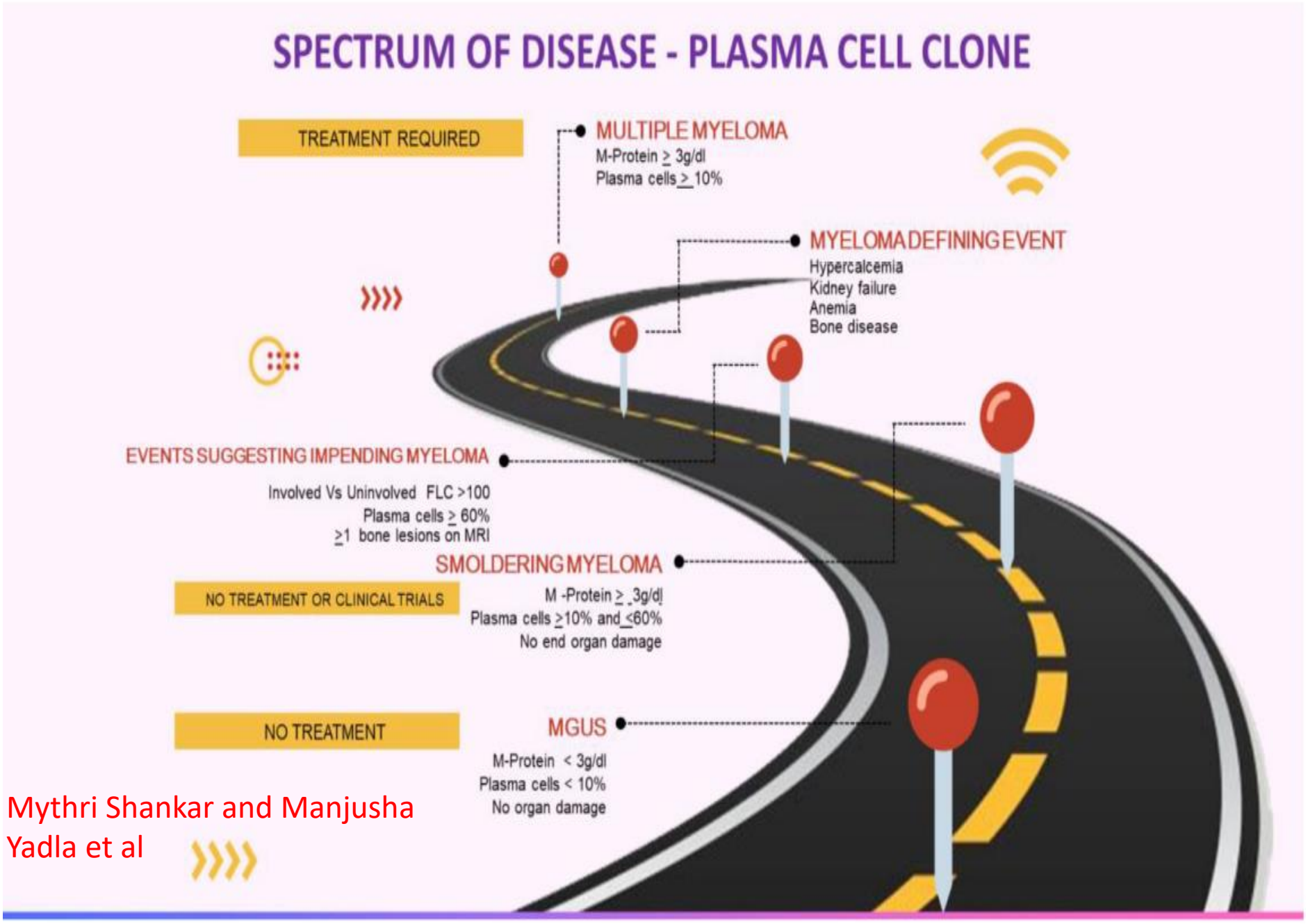
- AL amyloidosis commonly presents with nephrotic syndrome (albuminuria, hypoalbuminaemia and oedema) and relatively preserved renal function without hypertension.

- MIDD presents with nephrotic syndrome or significant proteinuria and CKD.

- Cryoglobulinaemic (type I or type II) glomerulonephritis presents as rapidly progressive glomerulonephritis (AKI and nephritic syndrome).

- Light chain proximal tubulopathy manifests with slowly progressive CKD, proteinuria and evidence of tubular dysfunction with Fanconi syndrome (normoglycaemic glycosuria, phosphaturia, uricosuria and proximal tubular acidosis).

SPECTRUM OF DISEASE - PLASMA CELL CLONE



Mythri Shankar and Manjusha Yadla et al

Table 1. *Definitions of B-cell and plasma cell proliferative disorders*

Plasma cell disorder	Criteria
Multiple myeloma	Clonal plasma cells in BM ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma, and any one or more of the following myeloma defining events[1]: - Hypercalcaemia: serum calcium > 0.25 mmol/l higher than upper limit of normal or > 2.75 mmol/l - Renal insufficiency: creatinine clearance <40 ml per min or serum creatinine > 177 µmol/l - Anaemia: (Hb < 6.2 mmol/l) - Bone lesions: one or more bone lesions on skeletal radiography, CT, or PET-CT Or any of the following biomarkers of progression[2]: - Clonal BM plasma cells ≥ 60% - 'Involved:uninvolved serum free light chain ratio' ≥ 100 - > 1 focal lesions on MRI studies
Smoldering multiple myeloma	Serum M-protein ≥ 30 g/l or urinary M-protein ≥ 500 mg/24 h and/or clonal BM plasma cells 10–60% Absence of SLiM-CRAB or amyloidosis
Waldenström's macroglobulinaemia	Lymphoplasmacytic infiltrate in BM ≥ 10% Serum monoclonal IgM of any level Symptoms of tumour mass/infiltration (adenopathy, anaemia etc) IgM-mediated symptoms can be present
Smoldering Waldenström's macroglobulinaemia	Lymphoplasmacytic infiltrate in BM ≥ 10% Serum monoclonal IgM of any level Absence of symptomatic tumour mass/infiltration (adenopathy, anaemia etc)
Non-IgM MGUS	Serum M-protein < 30 g/l Clonal plasma cells in BM < 10% Absence of SLiM-CRAB or amyloidosis
IgM MGUS	Serum IgM M-protein < 30 g/l BM involvement with lymphoplasmacytoid cells < 10% Absence of anaemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or any organ damage attributed to the lymphoproliferative disorder
Chronic lymphocytic leukaemia	Presence of ≥ $5x10^9$/l clonal B lymphocytes in peripheral blood Phenotype: CD5+, CD19+, CD23+, CD20+/-, sIg +/-
Monoclonal B lymphocytosis	Clonal B lymphocytes < $5x10^9$/l in peripheral blood Presence of CLL phenotype No evidence of lymphoma, infection, or autoimmune conditions

[1]Myeloma defining events: organ damage attributed to the underlying plasma cell disorder often abbreviated as 'CRAB' (hypercalcaemia, renal failure, anaemia, and bone disease).
[2]These three biomarkers are abbreviated to 'SLiM' (S ≥ 60% clonal plasma cells in BM; Li = light chains, kappa-to-lambda or lambda-to-kappa ratio ≥ 100; M ≥ 1 focal lesion by MRI).
BM = bone marrow; MGUS = monoclonal gammopathy of undetermined significance; M-protein = monoclonal protein; CLL = chronic lymphocytic leukaemia; Hb = haemoglobin; CT = computed tomography; PET-CT= positron emission tomography–computed tomography; MIR = magnetic resonance imaging; IgM = Immunoglobulin M; CD = cluster of differentiation; sIg = surface immunoglobulin

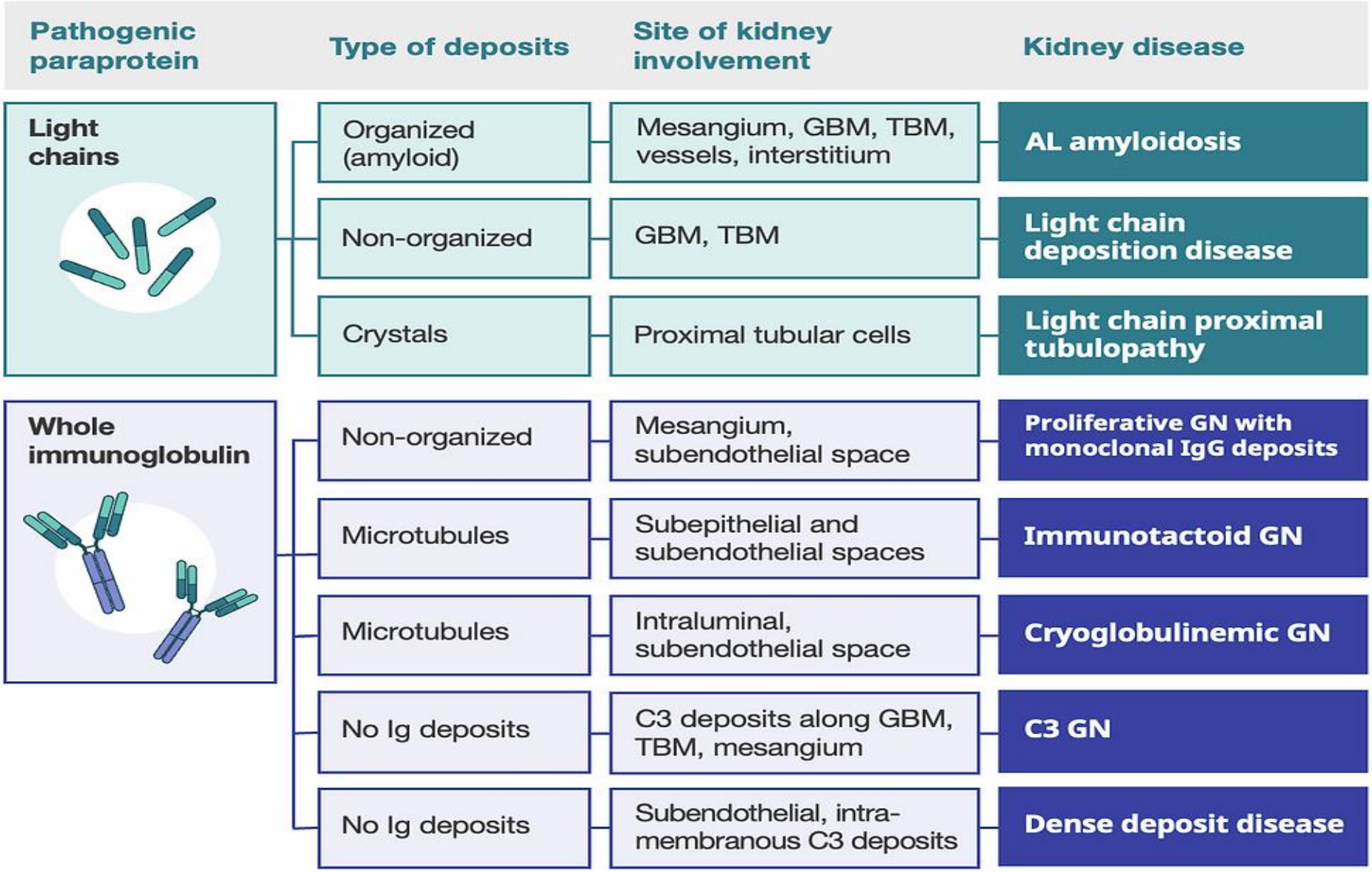
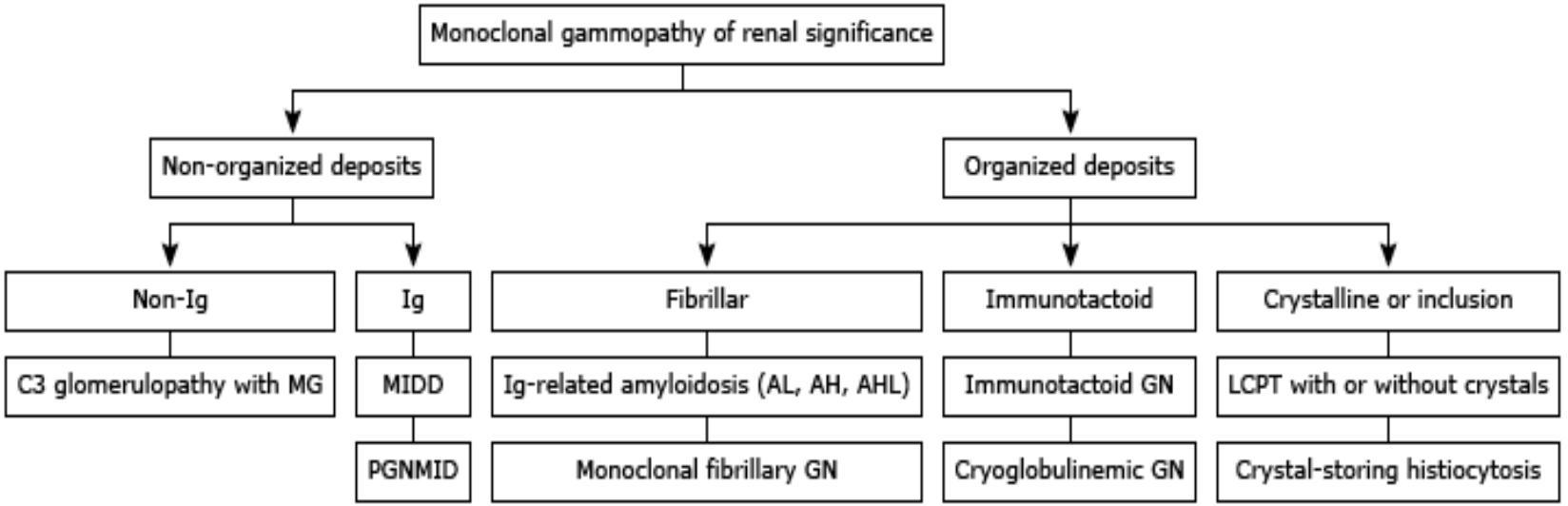


Figure 2. Spectrum of kidney pathology in monoclonal gammopathy of renal significance. GBM – glomerular basement membrane; GN – glomerulonephritis; TBM – tubular basement membrane.

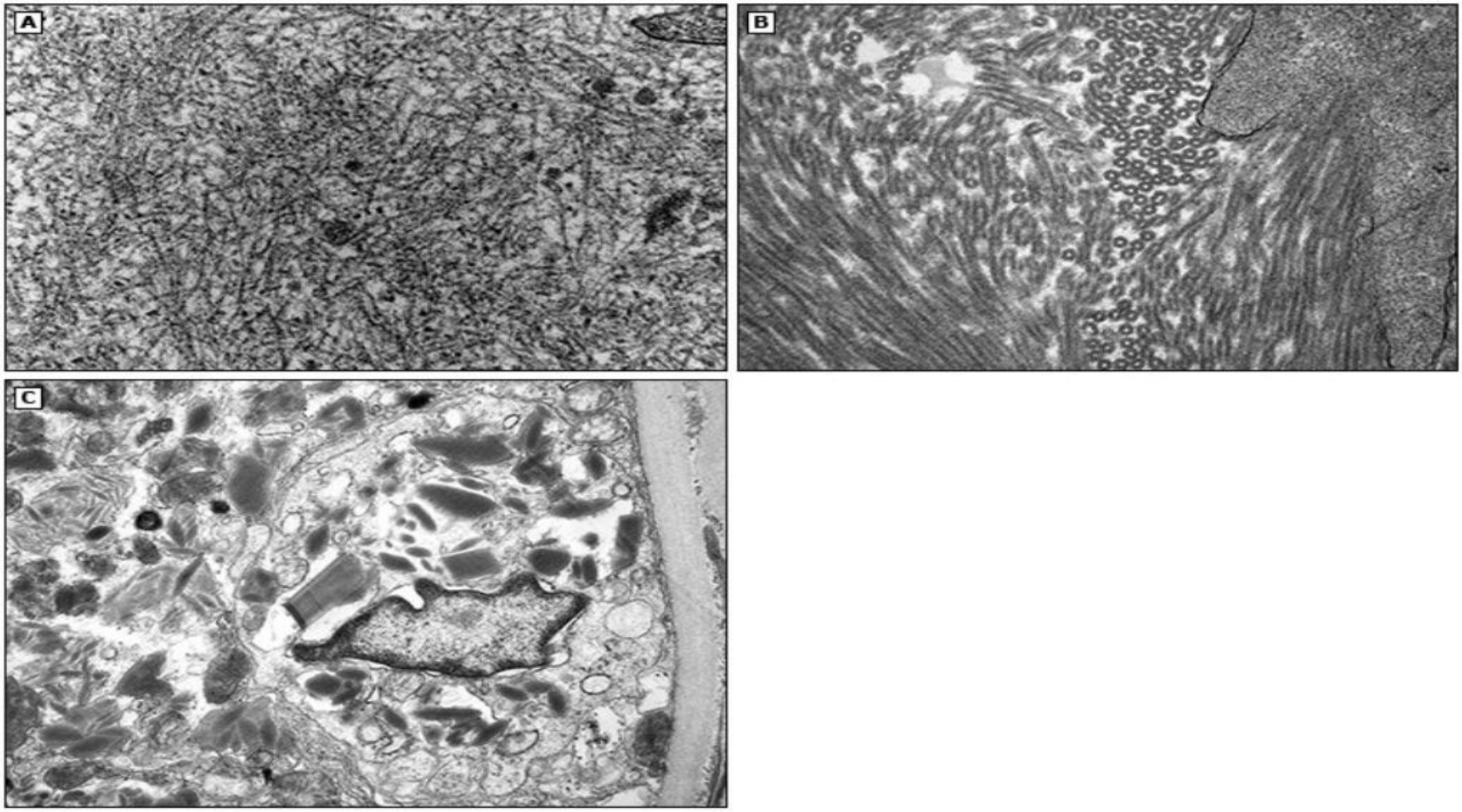
MGRS-associated kidney disease



MGRS: monoclonal gammopathy of renal significance; Ig: immunoglobulin; MG: monoclonal gammopathy; MIDD: monoclonal immunoglobulin deposition disease; AL: immunoglobulin light chain; AH: immunoglobulin heavy chain; AHL: immunoglobulin heavy and light chain; GN: glomerulonephritis; LCPT: light chain proximal tubulopathy; PGNMID: proliferative glomerulonephritis with monoclonal immunoglobulin deposits.

Classification based on electron microscopy of renal biopsy

MGRS lesions with organized deposits

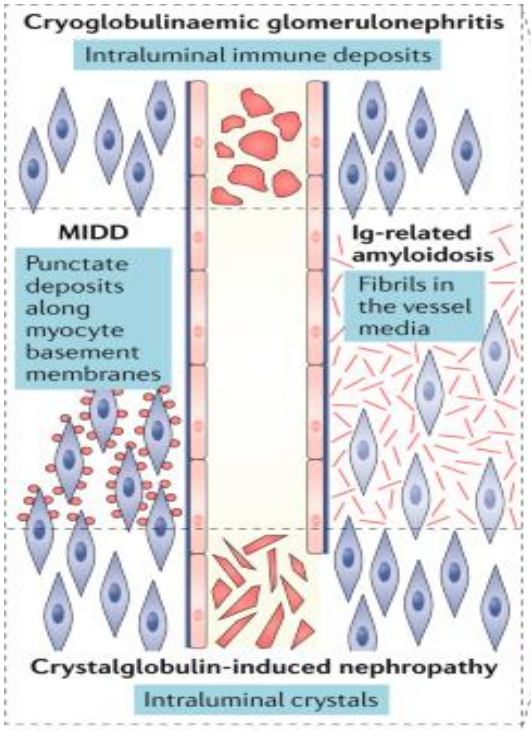


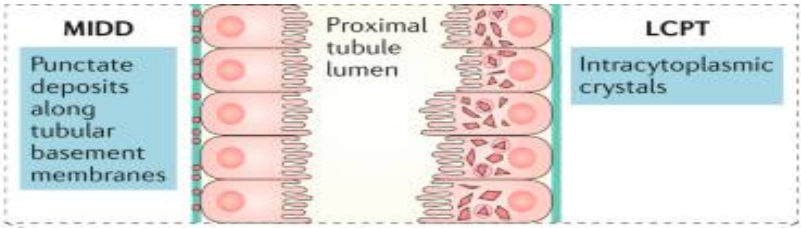
(A) Randomly arranged solid fibrillar deposits (diameter of 8 to 12 nm) in AL amyloidosis.

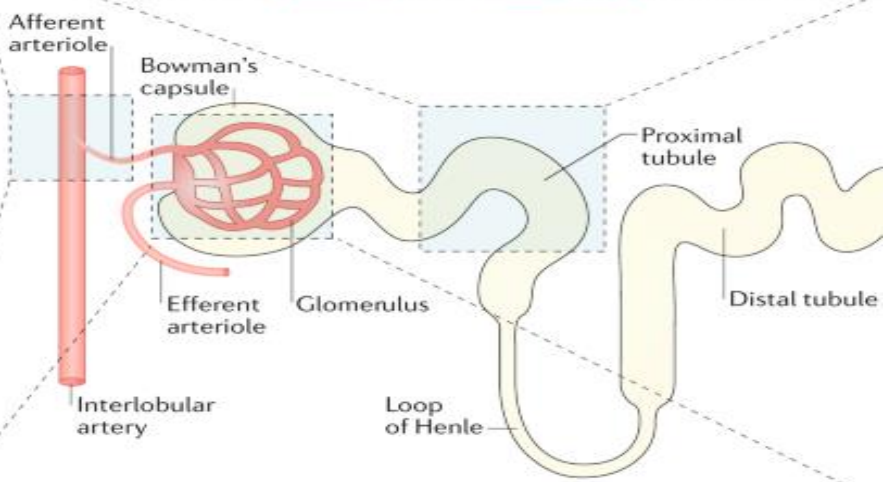
(B) Microtubular deposits (diameter of 17 to 52 nm), characterized by their hollow center, in immunotactoid glomerulopathy. They are commonly arranged in parallel arrays.

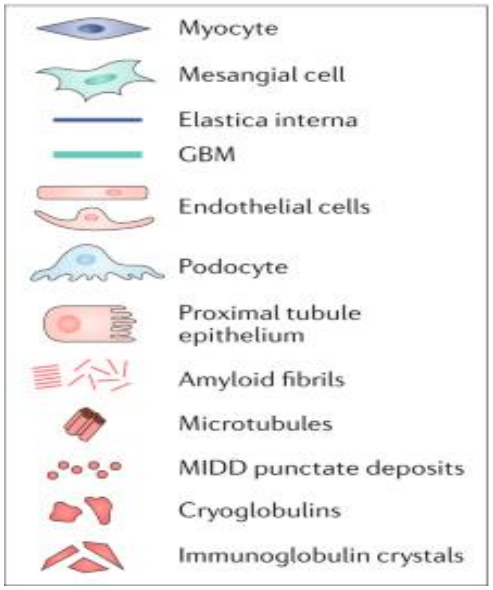
(C) Intracellular needle and rhomboid-shaped crystalline inclusions in light chain proximal tubulopathy.

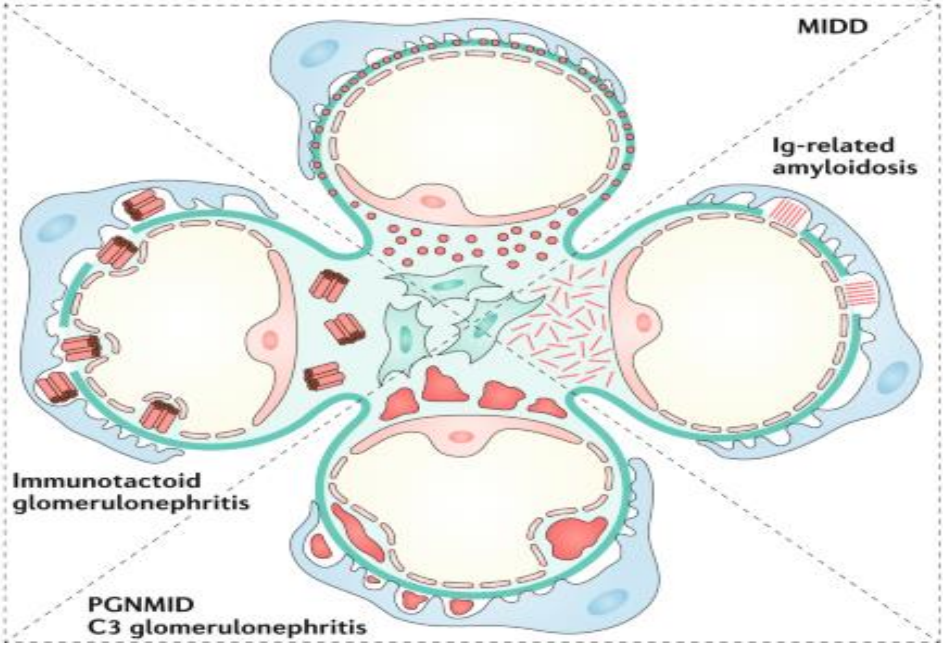
Localization of MGRS-associated renal lesions.











APPROACH TO MGRS

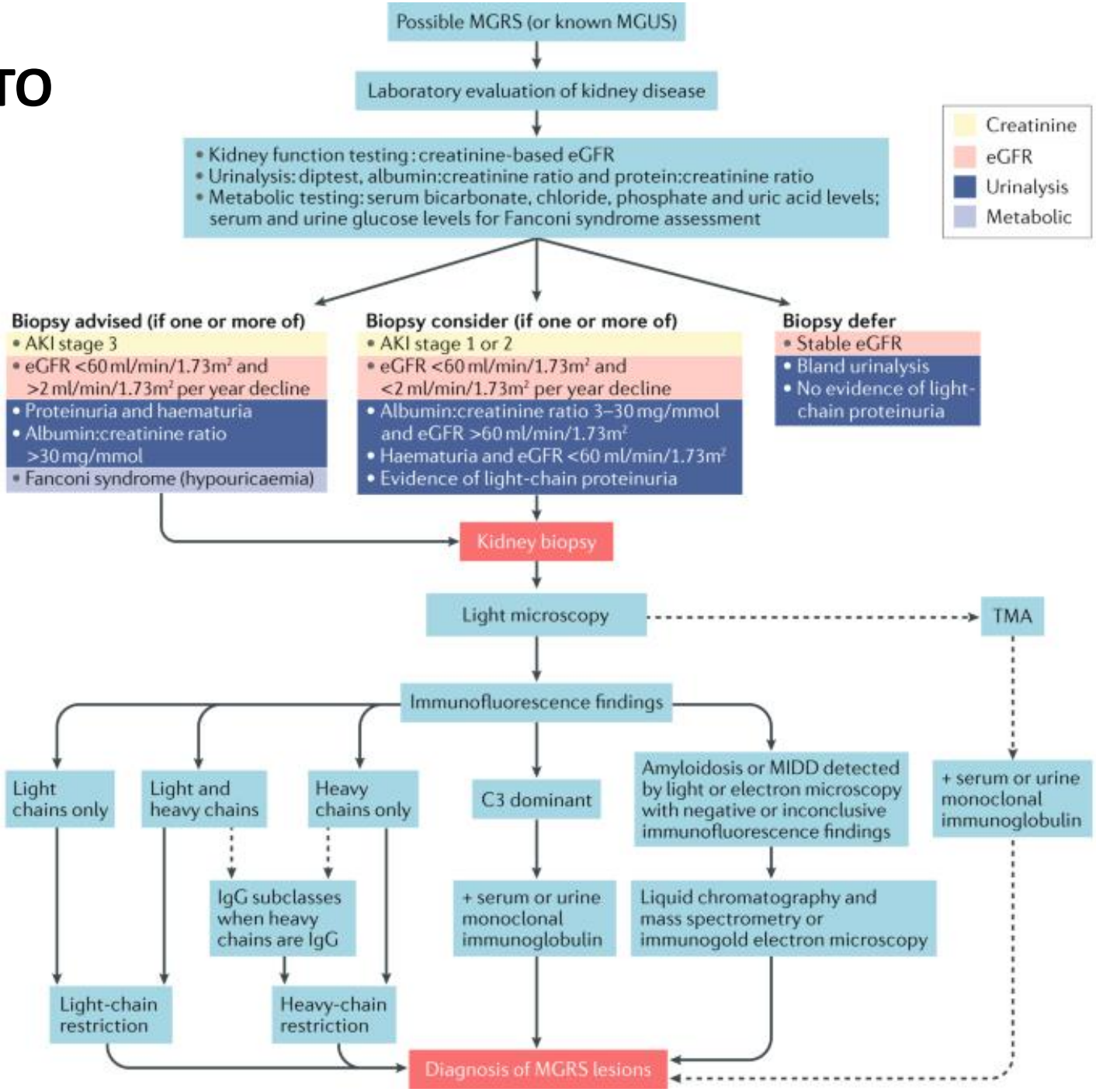


Table 3. *Overview of methods for monoclonal FLC detection*

	Serum protein EP	Urine protein EP	Serum IF	Urine IF	sFLC assay
Quantitative or qualitative	Semi-quantitative	Semi-quantitative	Qualitative	Qualitative	Quantitative: independent measurement of κ and λ FLC + calculation of a κ/λ ratio
FLC detection limit (sensitivity)	500-2000 mg/l	20-50 mg/l	150-500 mg/l	20-50 mg/l	κ: 1.5 mg/l λ: 3 mg/l
Advantages	Inexpensive; Easy to perform.	Inexpensive; Easy to perform.	10x more sensitive than serum PE.	-	Valuable as prognostic factor; Valuable for monitoring response to therapy.
Disadvantages	Low sensitivity for detection of low levels M-proteins, FLCs in particular.	FLCs in urine only when tubular reabsorptive capacity is overwhelmed; 24-hour urine collection required; Identification of monoclonal FLCs is a subjective interpretation of EP results; Difficult interpretation of EP results in concentrated urine or proteinuria.	-	FLCs in urine only when tubular reabsorptive capacity is overwhelmed 24-hour urine collection required.	More expensive; FLC assays are not accurate and measurements results are not equivalent between different methods; Assay reactivity of monoclonal and polyclonal κ and λ FLC in specific disease groups needs improvement.

EP = electrophoresis; IF = immunofixation; FLC = free light chain; sFLC = serum free light chain

TREATMENT OPTIONS

- ***Proteasome inhibitors***- Bortezomib, Carfilzomib, Ixazomib.
- ***Monoclonal antibodies*** - Rituximab, Daratumumab.
- ***Alkylating agents*** - Cyclophosphamide, Bendamustine, Melphalan.
- ***Immunomodulatory drugs***- Thalidomide, Lenalidomide, Pomalidomide.
- ***Glucocorticoids*** - Prednisone, Dexamethasone.
- In some patients (with amyloidosis or MIDD), the treatment strategy may also involve ***autologous hematopoietic cell transplantation.***