Highlights from IMW 2019

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Bologna
Royal Hotel Carlton

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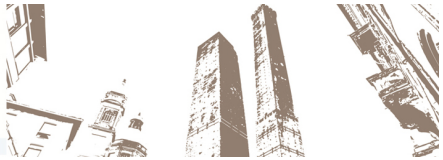
Gammapatie monoclonali di significato renale

Disclosures



Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Honoraria
Janssen							x
Celgene							x
Amgen							x
Takeda							x

Definitions

M onoclonal
G ammapathy
R enal
S ignificance

Plasma cell clone: IgG > IgA > (IgD), LC only
B-cell / lymphoplasmacytic clone: IgM > IgG
MIg: intact Ig, LC, LC+HC, HC only

monoclonal gammapathy
BUT no overt diagnosis of symptomatic MM / WM / CLL

+

associated symptoms / renal damage
related to MIg or clone by any mechanism other than tumor burden

current haematological criteria for specific therapy are not met

Bridoux et al. Kidney International 2015
Leung et al. Nat Rev Nephrol 2019
Fermand et al. Blood 2013; Blood 2018

Prognostic considerations

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

Blood. 2012;120(22):4292-4295

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

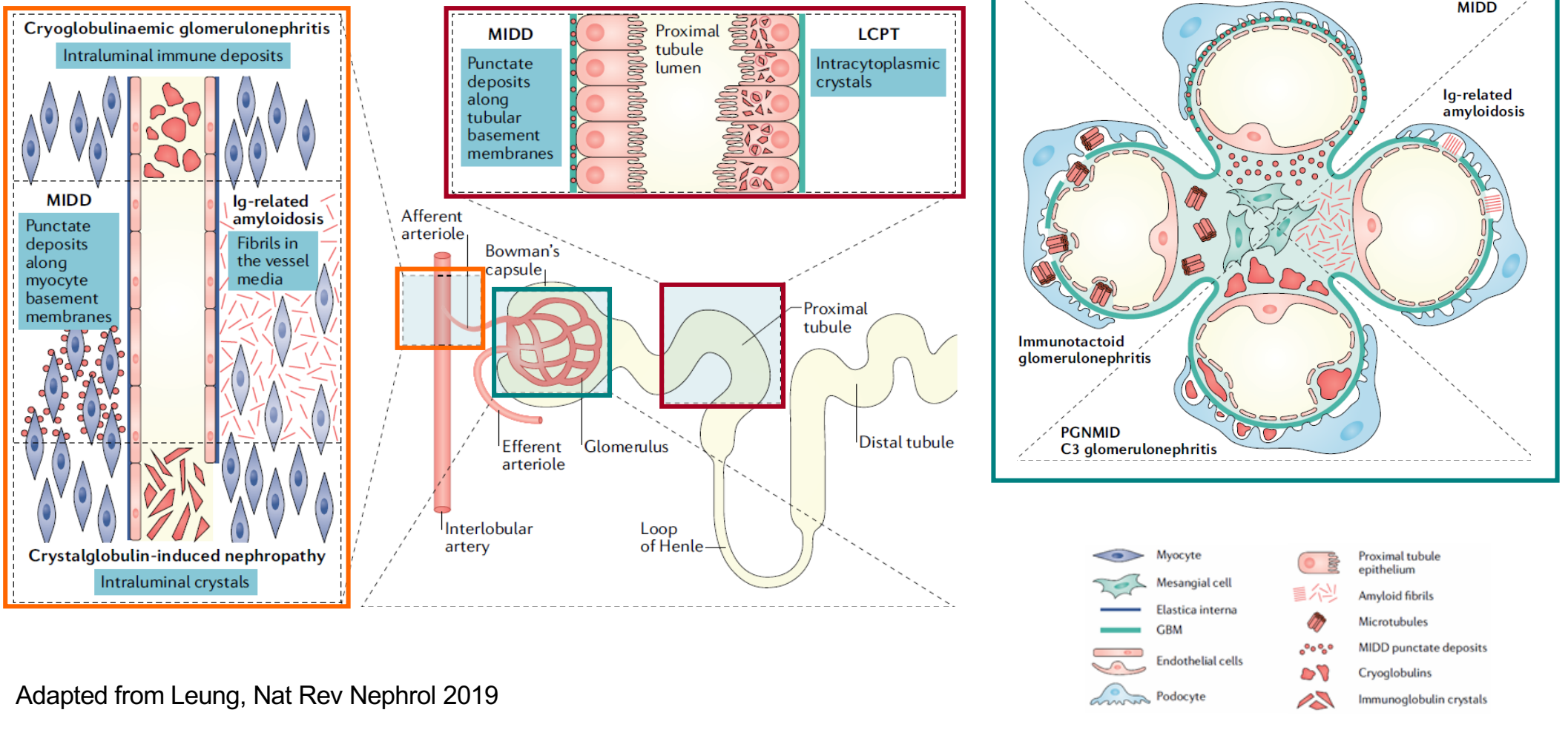
Monoclonal gammopathy: The good, the bad and the ugly

Siobhan V. Glavey [a], Nelson Leung [b,c,*]

Blood Reviews 30 (2016) 223–231

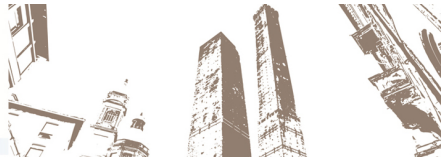
- Still poorly recognized and frequently undertreated
- Potentially severe organ damage → ESRD
- High rates of recurrence after kidney transplantation
- Efficient suppression of nephrotoxic MIg can impact renal and patient survival

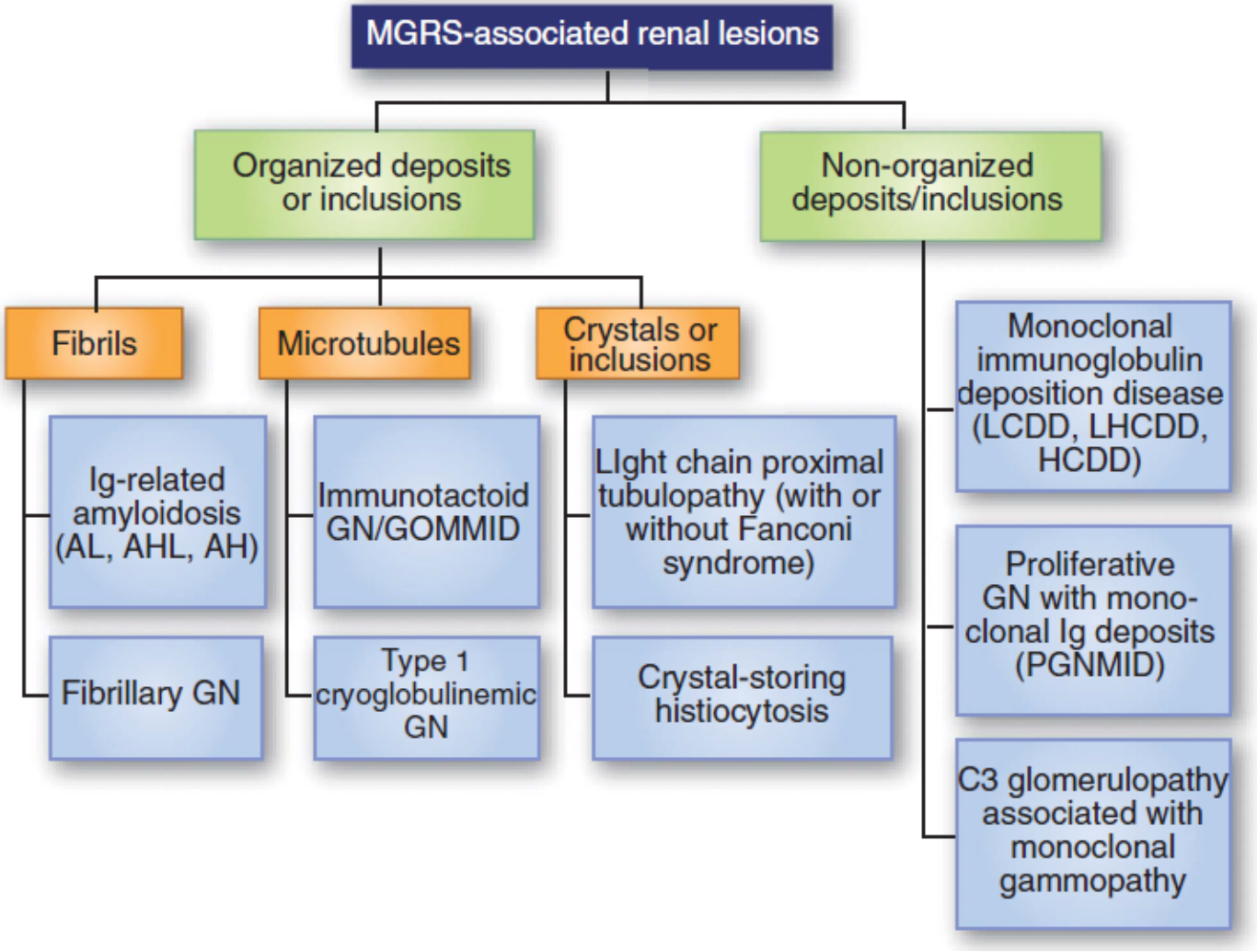
MGRS-associated renal lesions



Adapted from Leung, Nat Rev Nephrol 2019

Histopathologic classification





MGRS	Involvement		MG	Renal biopsy findings		
	renal	extrarenal		LM	IF/IHC	EM
AL amyloidosis	Glomeruli, vessels, interstitium	Heart, liver, GI, peripheral nerve, soft tissues	λ LC (75%) k LC (25%)	Amorphous/acellular mesangial deposits, PAS/ silver neg; Congo Red pos	AL: LC restriction (mostly λ)	Randomly oriented nonbranching fibrils (8-12 nm Ø)
Fibrillar GN	Mesangium, capillaries	/	IgG (policlonal)	Mesangial proliferation, MPGN pattern, Congo Red neg	IgG (++ IgG1), 15% monoclonal	Randomly oriented nonbranching fibrils (12-24 nm Ø)
Immunotactoid GN	Glomeruli	/	CLL-like (50%)	Membranous or MPGN pattern	IgG with LC restriction, C3, occasional IgM	Organized parallel microtubules (> 30 nm Ø)
Type I (type II) cryoglobulinemic GN	Glomeruli, vessels	Skin, peripheral nerve, joints	IgG/IgM	MPGN pattern, endocapillary GN, PAS+, intraluminal deposits	Granular deposits in mesangium/capillaries; IgG > IgM, k>l, C3-C4, C1q	Subendotelial and intracapillary deposit, frequently microtubular (10-90 nm Ø)
Light chain proximal tubulopathy (LCPT) (w/o Fanconi)	Tubules, interstitium	/	K LC (>90%)	PTC vacuolation/fragmentation; intracytoplasmatic inclusion (often crystalloid)	LC (k) inclusions within tubular epithelium	Intralysosomal or free romboid-shaped crystals in proximal tubules
Cristal storing histiocytosis	Interstitium	Cornea, joints, lymphoid tissue	K LC	Interstitial infiltration of histiocytes/macrophages with eosinophilic inclusions	LC (k) Crystalloid inclusions within histiocytes/ macrophages	Rhomboid/needle-shaped crystals and vacuoles within interstitial histiocytes/macrophages
MIDD: Monoclonal Ig deposition disease (LCDD, LHCDD, HCDD)	Glomeruli, tubules, vessels	Heart, liver, lung	LCDD: usually k LC	Mesangial proliferation, nodular glomerulosclerosis, thickening of TBM, congo red neg	Diffuse linear deposit along GMB, TBM, arteriolar/ arterial myocytes (k LC)	Punctate powdery electron-dense deposit along inner aspect of GBM and outer TBM
Proliferative GN with monoclonal Ig deposit (PGNMID)	Glomeruli	/	IgG (++IgG3)	Endocapillary proliferative GN; MPGN	Glomerular granular deposit of MIg with LC restriction (mesangium and capillary wall)	Nonorganized mesangial, subendothelial electron-dense deposit; less common subepithelial
C3 glomerulopathy associated with MG	Glomeruli	/	(IgG)	Endocapillary proliferative GN; MPGN	Granular C3 deposit in mesangium and capillaries. Absence of Ig deposit. Pronase treatment to detect MIg	Mesangial, intramembranous and subendothelial electron-dense deposit

Pathogenesis

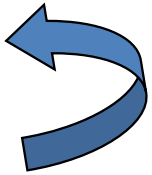
Structural characteristics and physicochemical properties of the MIg are the main determinants of renal lesions

Direct mechanism: MIg deposition

Intact Ig molecules are entrapped in glomeruli, LC/truncated HC can potentially affect all renal compartments

- induction of (myo)fibroblast phenotype in glomerular mesangial cells → excessive matrix secretion (glomerulosclerosis/MP appearance)
- deposition of large amounts of fibrillar material → compression/atrophy
- activation of apoptotic, proinflammatory and fibrotic pathways

subversion of tissue architecture → organ dysfunction



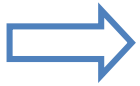
- LC excess and crystalline inclusions within PTCs → interference with membrane transporters/ lysosomial function → disrupted reabsorption capability

Pathogenesis

Indirect mechanism: autoantibody activity of MIg

- against complement regolatory proteins (complement factor H, factor B/C3 nephritic factor)

increased half-life of C3 convertase
hyperactivation of alternative pathway of complement
dysregulation of CAP



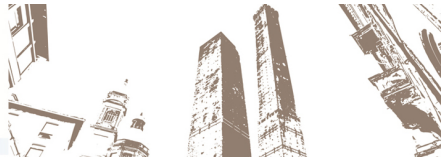
C3GN

- monoclonal IgM presenting with rheumatoid factor activity (mixed type II cryoglobulinemias)

Unknown / putative mechanism

Absorption of biologically active molecules in clonal cells or aggregated MIg
(factor X absorbtion on AL amyloid fibrils → bleeding disorders)

Clinical presentation



MGRSs may show a wide range of manifestations, depending on the underlying pathogenic mechanism and the primary site of involvement

Renal findings

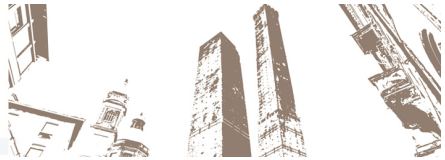
- Various degrees of renal impairment up to ESRD
- Different degrees of proteinuria, which may reach nephrotic range
- Nephritic syndrome (hematuria, hypertension, edema)
- Electrolyte abnormalities
- Signs of PTCs dysfunction (glycosuria, aminoaciduria, phosphaturia, acidosis)

Clinical presentation

Extrarenal manifestations

- Amyloidosis-related
  - Heart: restrictive cardiomyopathy with heart failure and preserved ejection fraction, arrhythmias
  - Soft tissues: carpal tunnel syndrome, macroglossia, shoulder pad, and soft-tissue swelling/masses
  - Liver: hepatomegaly, ↑↑ alkaline phosphatase, liver function test abnormalities
  - Peripheral and/or autonomic nervous system: sensory-motor axonal PN, orthostatic hypotension
  - Gastrointestinal tract: altered motility, bleeding, malabsorption
- Cutaneous/vascular: petechiae/purpura, Raynaud's phenomenon, hyperviscosity, vasculitis
- Ocular: keratopathy, maculopathy
- Poliarthralgia
- Osteomalacia

Diagnostic considerations



1. When to suspect a MGRS

MGRS should be considered in every pt with renal manifestations combined with an M-protein

2. Exclude a chance association

Not every pts with MG and kidney disease has MGRS!

- high prevalence of MG in the elderly + high incidence of chronic kidney disease after age 60

  → rule out cardiovascular/metabolic risk factors/disease

- hereditary/senile amyloidosis with MIg

3. Establish causal relationship between MG and clinical manifestation

Demonstration of a MIg deposition in affected tissue/organ that matches circulating MIg

For MIg-mediated immune process: complement abnormalities, high titer of autoantibody activity

Clinical evidence as “surrogate causal link”: response to therapy targeting MIg secreting clone

Diagnostic workup

KIDNEY BIOPSY

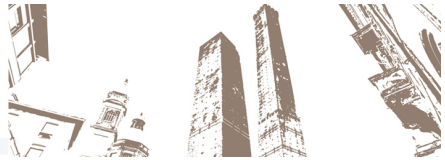
- **LM**: morphological alteration, PAS/Congo-Red staining
- **IF/IHC**: Ab specific for LC and Ig isotypes, IgG subclasses, complement
- **EM**: ultrastructural characterization, composition and pattern of distribution of deposits
- Ancillary techniques:
  - laser microdissection followed by liquid chromatography and mass spectrometry (amyloid typing)
  - paraffin immunofluorescence after protease digestion (masked antigens, intracellular deposits or C3GN)

IDENTIFICATION OF PARAPROTEIN

- serum and urine electrophoresis
- serum and urine immunofixation
- serum light chain assay → normal FLC ratio k/λ 0.26-1.65
  "renal range" FLC ratio k/λ: 0.37-3.17

assessment of hematological response

Diagnostic workup



CLONAL IDENTIFICATION

- bone marrow aspirate/biopsy +/- IHC and flow cytometry
  - → to identify/quantify the underlying B cell or plasma cell clone
  - → to exclude overt MM / WM
- lymphnode biopsy: in pts with IgM or high suspition for lymphoma

IMAGING STUDIES

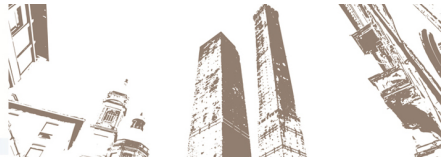
CT scan with or without PET; whole-body/axial MRI

- → to look for localized plasmacytoma or lymphadenopathy in low-stage/low-grade lymphoma in pts with "negative" bone marrow evaluation
- → to look for bone disease/focal lesions for pts with suspected MM

IDENTIFICATION OF EXTRARENAL INVOLVEMENT

- cardiac evaluation (echocardiogram, cardiac MRI, NT-proBNP and troponin levels)
- nerve conduction studies
- skin biopsy
- GI endoscopy...

Treatment



Aimed at:

eradication of secretory clone
(although not malignant per se)
to preserve/improve organ function
reduce the risk of disease recurrence after transplantation

Driven by:

- organ damage/organ involved
- type of underlying clone
- comorbidities
- natural disease history
- metabolism and safety profile of antineoplastic drugs in RI

Treatment

AL amyloidosis: cardiac involvement is critical, guidelines and clinical trials available

Plasmacytic clone secreting IgG/IgA or LCs only: **strategy based on anti-MM agents**

- **bortezomib**, usually in combination with dexa and cyclophosphamide (CyBorD regimen)
- **HDM + ASCT**, upfront or after a bortezomib-based induction
- local radiotherapy (if clone responsible for MGRS manifest as a solitary plasmacytoma)
- IMiDs in the relapse setting

B-cell clone (lymphoplasmacytic with IgM production, B cell lymphoma, CLL):
→ antiCD20 monoclonal antibody

- **Rituximab** in combination with either cyclophosphamide or bendamustine
- no clear data on new/non conventional agents
- plasmaexchange/antiviral therapy in crioglobulinemia with rapidly progressive renal disease/HCV+

Treatment

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

Take home messages

- Wide spectrum of rare renal diseases with potential severe organ (and systemic) damage → early detection is key
- Organ damage is indipendent from clonal mass
- Histopathologic identification and classification crucial for determining the optimal treatment
- Efficient control of underlying clone can impact renal and patient survival

Multidisciplinary approach is required:
haematologists, nephrologists and (nephro)pathologists