Renal Crystalline Induced Glomerulopathy

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Disclosure of Relevant Financial Relationships

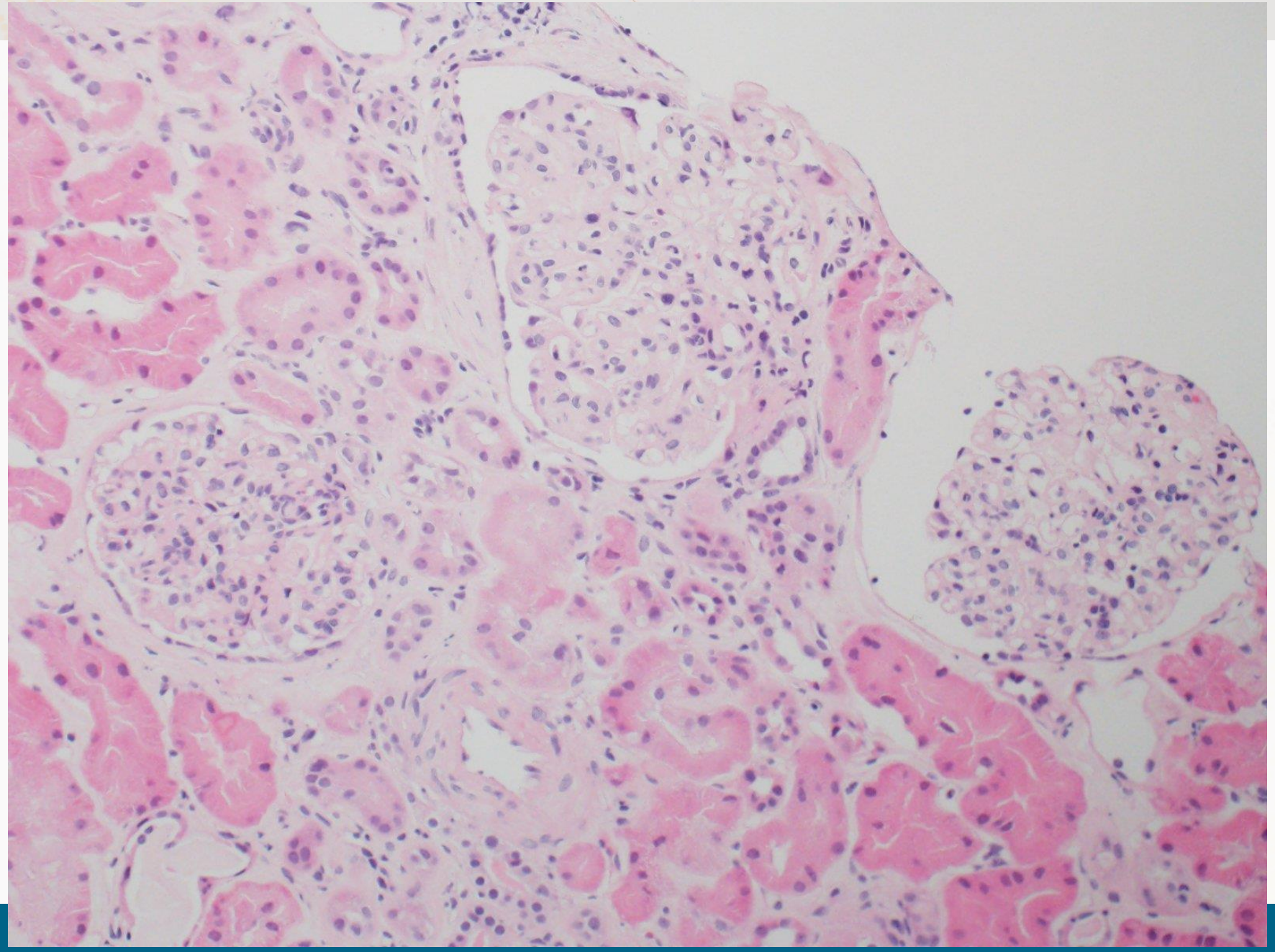
No relevant financial relationships

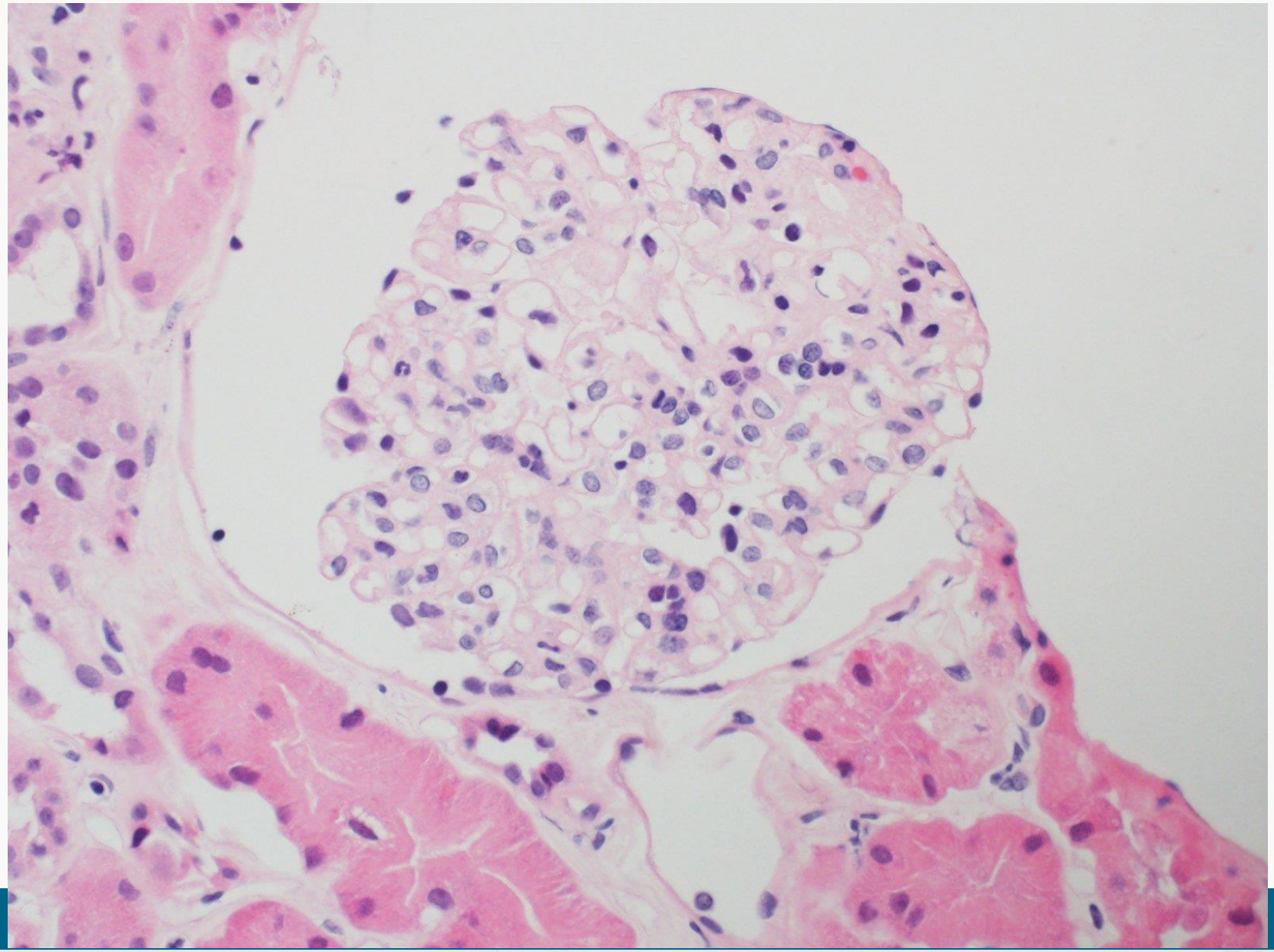
Clinical Information

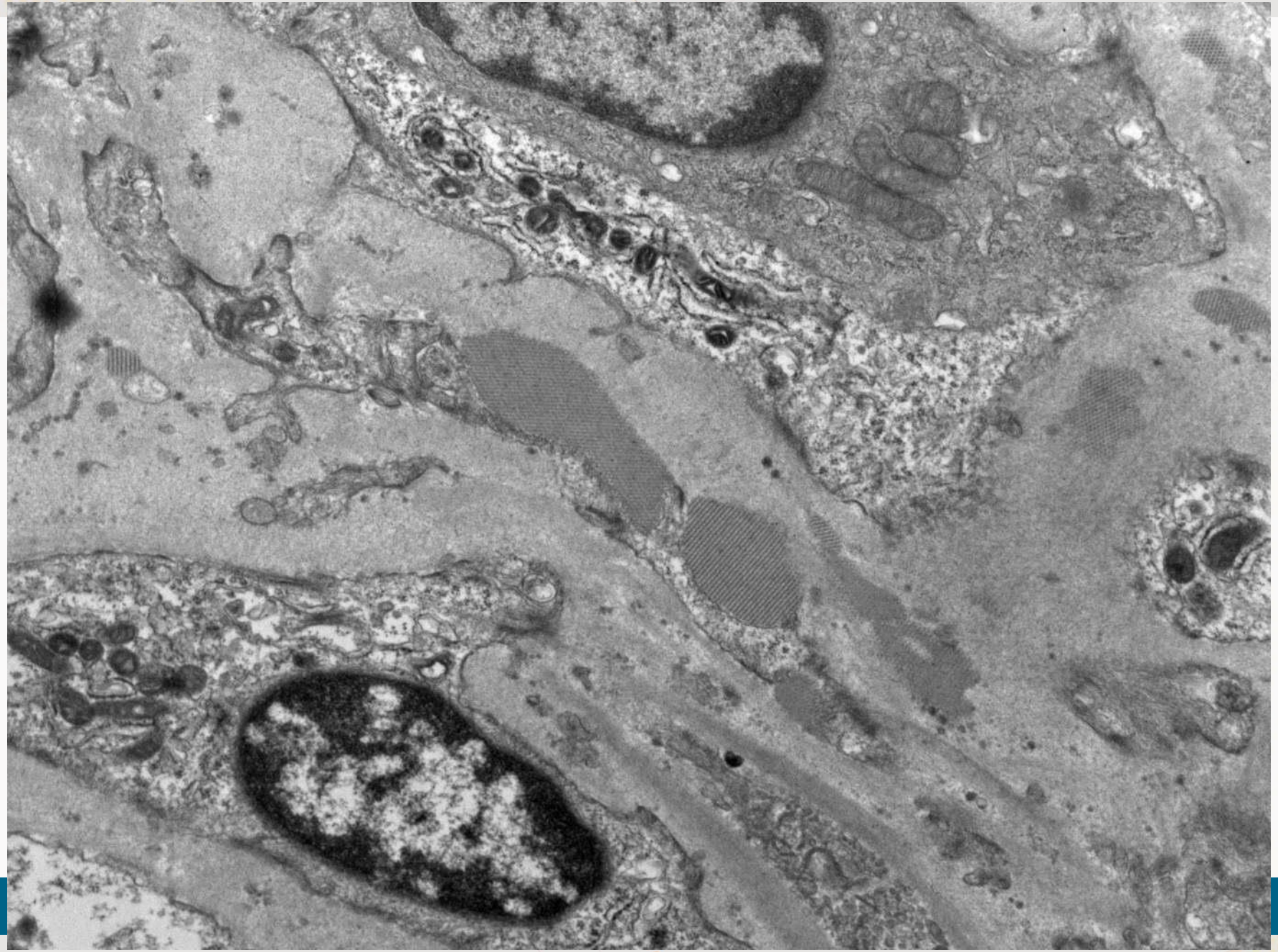
- A 73-year-old man presented with history of increasing proteinuria
- Nephrotic range proteinuria 3 grams/day
- Creatinine of 127 mg/dl

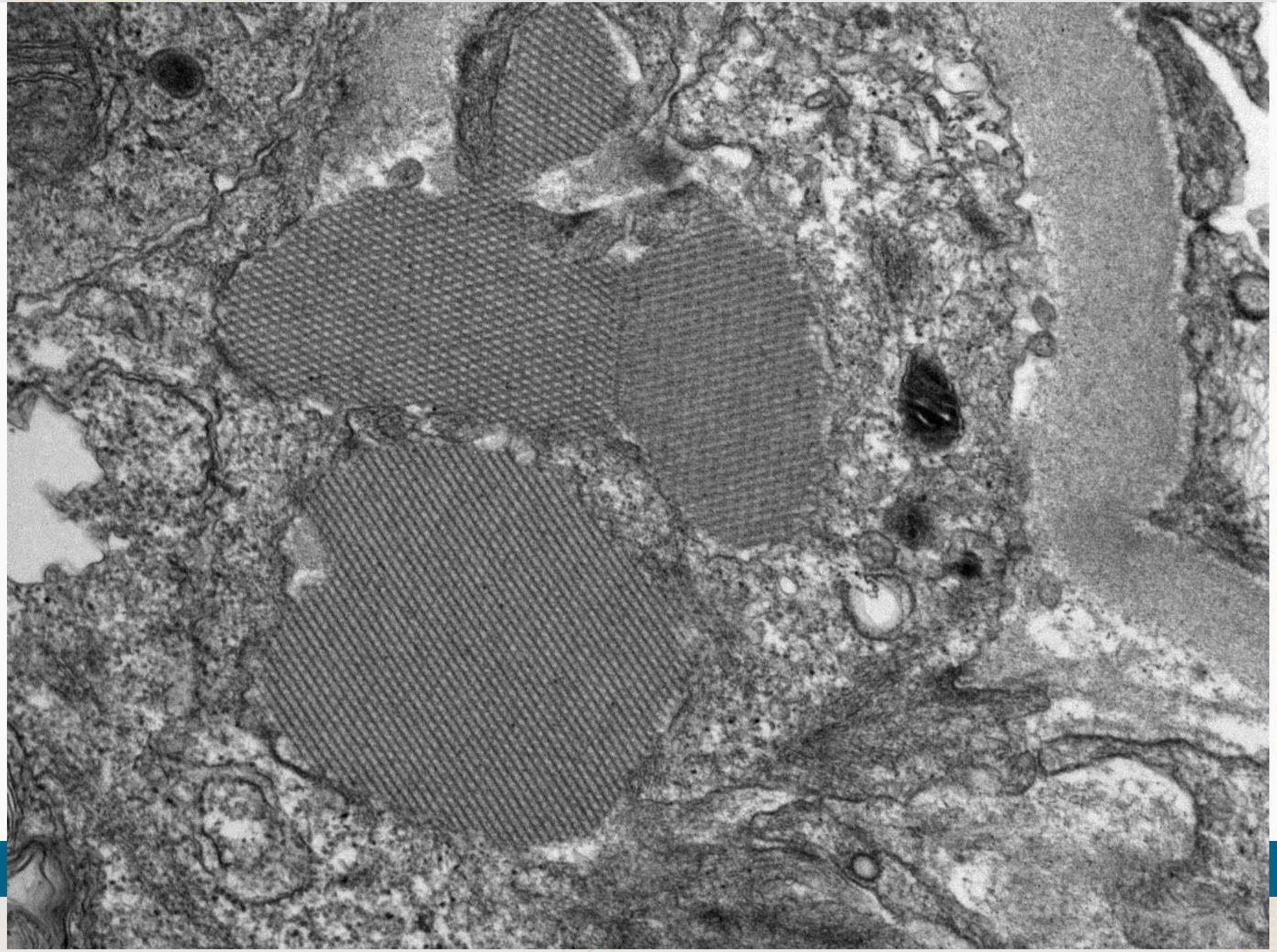
- No paraprotein detected in serum electrophoresis
- Autoimmune serology was negative

- Hypertension (well controlled)









Immunofluorescense

Standard immunofluorescence all negative

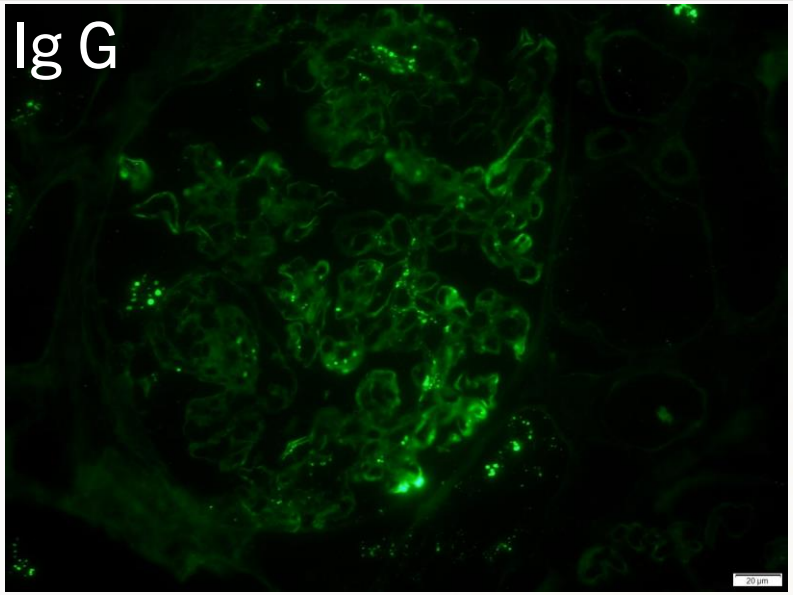
Paraffin immunofluorescence (IF) pronase digestion

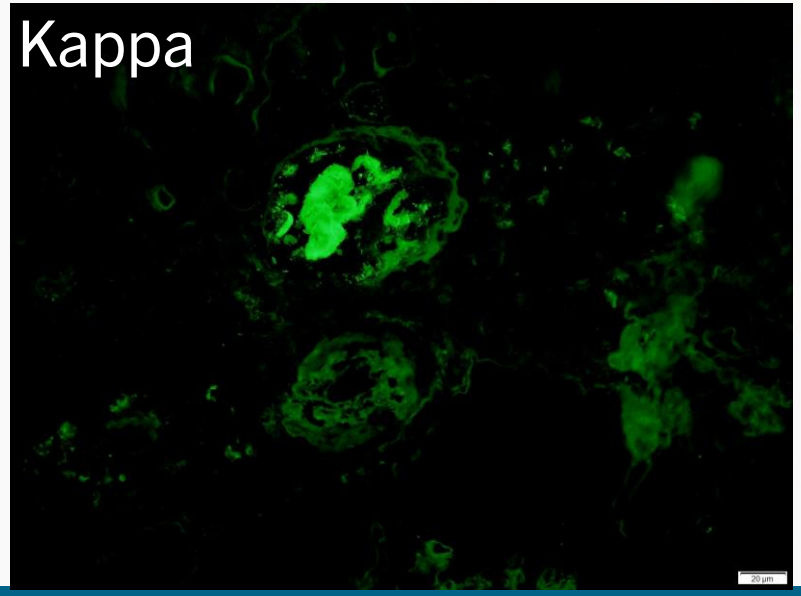
IgG and kappa ++/+++ →kappa restricted crystals.

IgA, C1q, C3,lambda (-)

IgM trace

Vessels (-)





Diagnosis

Renal crystalline induced nephropathy

Raising the possibility of small kappa monoclonal gammopathy of renal significance (MGRS)

Subsequent repeat electrophoresis by gold immunofixation detected kappa monoclonal IgG in serum and the above diagnosis was confirmed.

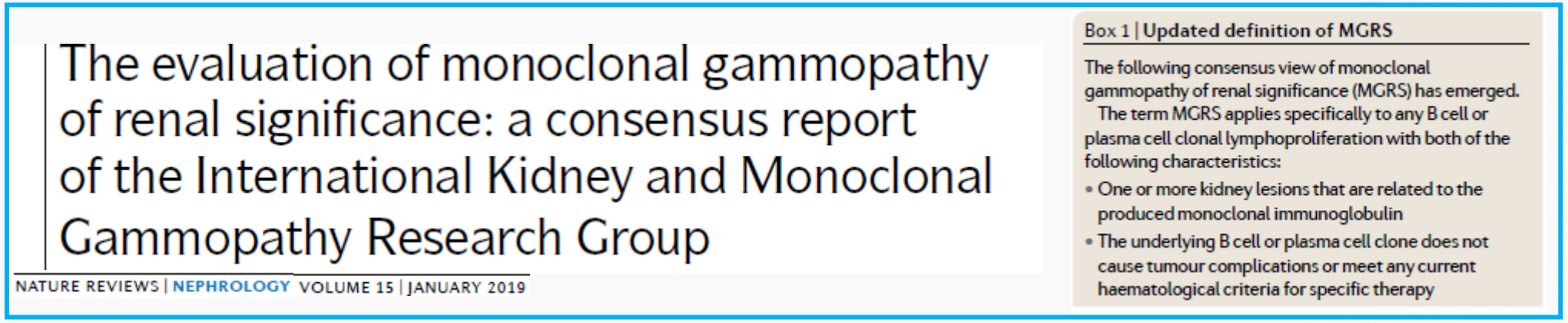
Clinical Progress

- Haemodialysis
- Then started on bortezomib, and dexamethasone

- Repeat renal biopsy one year later showed
  - MPGN-like pattern
  - No increase in cellularity or exudation of inflammatory cells
  - The paraffin IF with pronase digestion and electron microscopy showed no crystals and no deposits.
  - The glomerular scarring still remained at 30%.

Renal Crystalline Induced Nephropathy

- Monoclonal gammopathy of renal significance (MGRS) associated disease → clone directed therapy
- Also can be associated with multiple myeloma



The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group

NATURE REVIEWS | NEPHROLOGY VOLUME 15 | JANUARY 2019

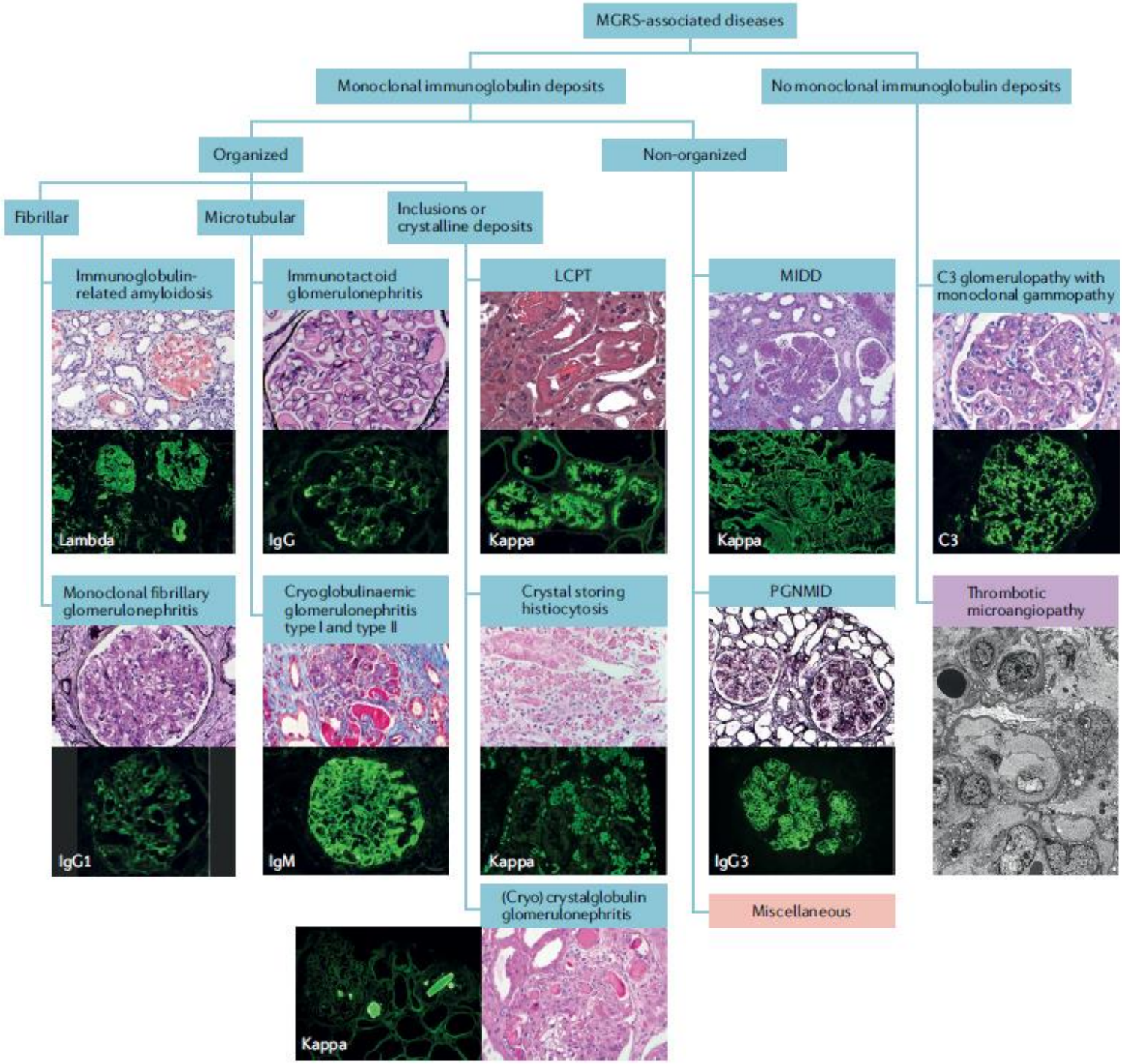
Box 1 | Updated definition of MGRS

The following consensus view of monoclonal gammopathy of renal significance (MGRS) has emerged.

The term MGRS applies specifically to any B cell or plasma cell clonal lymphoproliferation with both of the following characteristics:

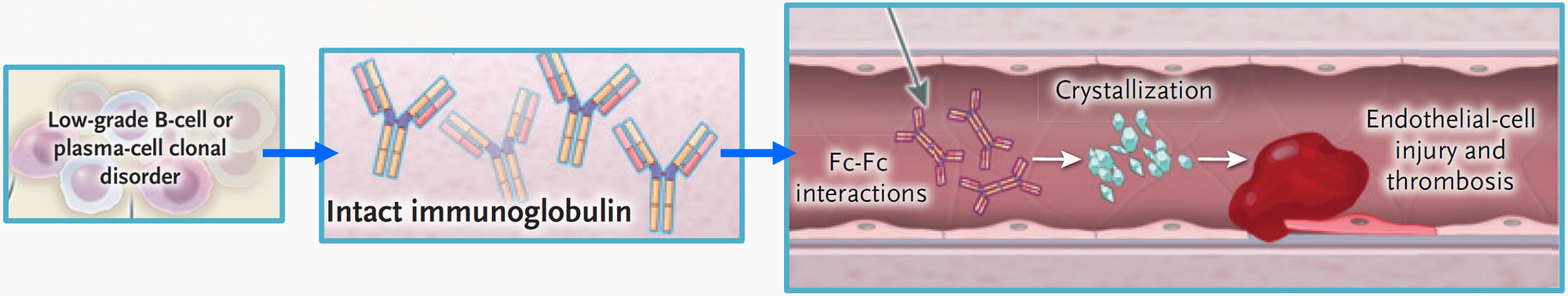
- One or more kidney lesions that are related to the produced monoclonal immunoglobulin
- The underlying B cell or plasma cell clone does not cause tumour complications or meet any current haematological criteria for specific therapy

Leung et al, 2019



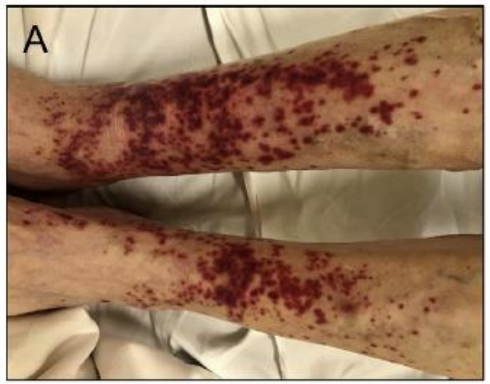
Leung et al, 2019

Cystalglobulinemia



Modified from Leung et al, 2021

- Kidneys and skin are main organs to get involved.
  - Thrombotic microangiopathy, acute kidney disease, nephrotic syndrome and eventually leading to end stage kidney disease
  - Cutaneous manifestations can be rash or purpuric lesions



Leflot et al, 2022

Characteristics of Patients with Crystalglobulin-associated nephropathy (3)

		Baseline Characteristics				Extrarenal Manifestations			Hematologic Disorder		Treatment			Outcome		
Pt	Ref	Sex	Age, y	sCreat, mg/dL	Dialysis	Any	Skin	Joints	MIg	Disease	Chemotherapy	Steroids Alone	Plasma Exchange	FU, mo	Death	Kidney Failure
1	3	M	52	14.7	+	-	-	-	IgGλ	MM	-	-	-	0.1	+	+
2	3	M	58	22.2	+	+	-	-	IgDλ	MM	Mel	-	+	1.7	+	+
3	4	M	82	4.3	+	+	+	+	FLCλ	MM	-	+	-	0.5	+	+
4	4	F	34	8.4	+	+	+	+	FLCλ	MM	Cy	-	+	0.6	+	+
5	5	M	51	4.1	+	+	+	+	IgGκ	MGRS	-	+	-	41	-	+
6	6	M	44	17.3	+	+	+	-	IgGκ	MGRS	BorD	-	+	12	-	+
7	2	F	61	5.2	+	+	+	-	IgGκ	MGRS	CyBorD	-	+	7	-	-
8	7	M	53	2.4	+	+	+	-	IgGκ	MGRS	Bor/Cy	-	+	19	+	+
9	8	M	44	6.3	+	+	+	-	IgGκ	MGRS	Unknown	-	+	15	+	+
10	9	M	56	5.4	-	+	-	+	IgGλ	MGRS	CyBorD	-	+	12	-	-
11	10	M	50	8.1	+	+	+	+	IgGκ	MGRS	Bor	-	+	NA	-	-
12	11	F	61	3.8	-	-	-	-	IgAλ	MGRS	CyBorD	-	+	NA	-	-
13	12	F	49	3.7	-	-	-	-	IgGκ	MGRS	CyBorD	-	+	9	-	-
14	13	F	74	4.2	+	+	+	+	IgGκ	MGRS	CyBorD	-	+	32	-	-
15	14	F	65	4.3	+	-	-	-	IgMκ	MGRS	-	+	-	2	-	+
16	15	F	40	4.4	+	+	+	-	IgGκ	MGRS	BorD/PD	-	+	180	-	+
17	16	M	63	4.1	+	+	-	+	IgAκ	MGRS	-	-	-	NA	-	+
18	17	F	66	5.9	+	+	+	-	IgGκ	MGRS	BorD	-	+	48	-	-
19	18	F	70	1.8	-	-	-	-	IgAκ	MM	CyBorD	-	+	6	-	-
20	Present	F	69	5.3	+	+	+	+	IgGκ	MGRS	CyBorD/LBorD	-	+	18	-	+

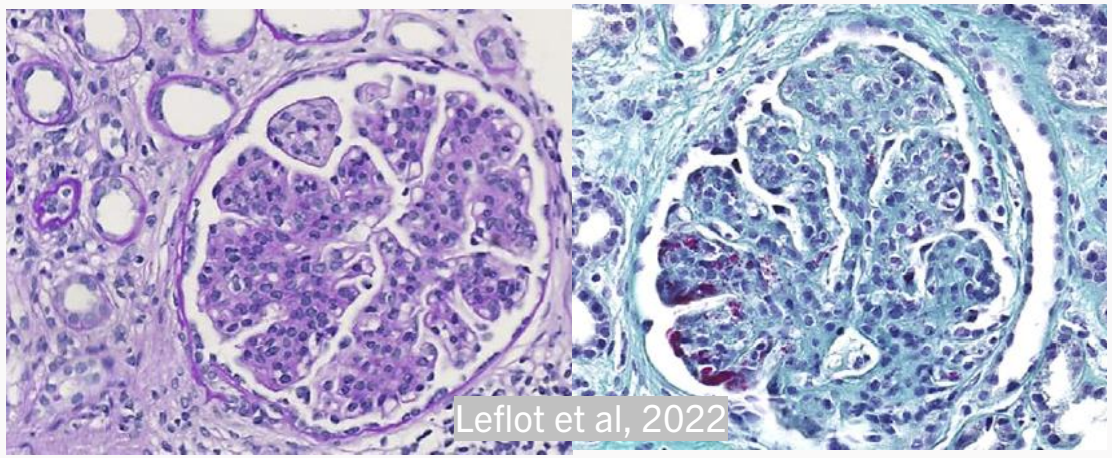
Abbreviations: Bor, bortezomib; Cy, cyclophosphamide; D, dexamethasone; F, female; FLC, free light chain; FU, follow-up; L, lenalidomide; M, male; Mel, melphalan; MGRS, monoclonal gammopathy of renal significance; MIg, monoclonal immunoglobulin; MM, multiple myeloma; NA, not available; P, pomalidomide; Pt, patient; Ref, reference; sCreat, serum creatinine.

Leflot et al, 2022

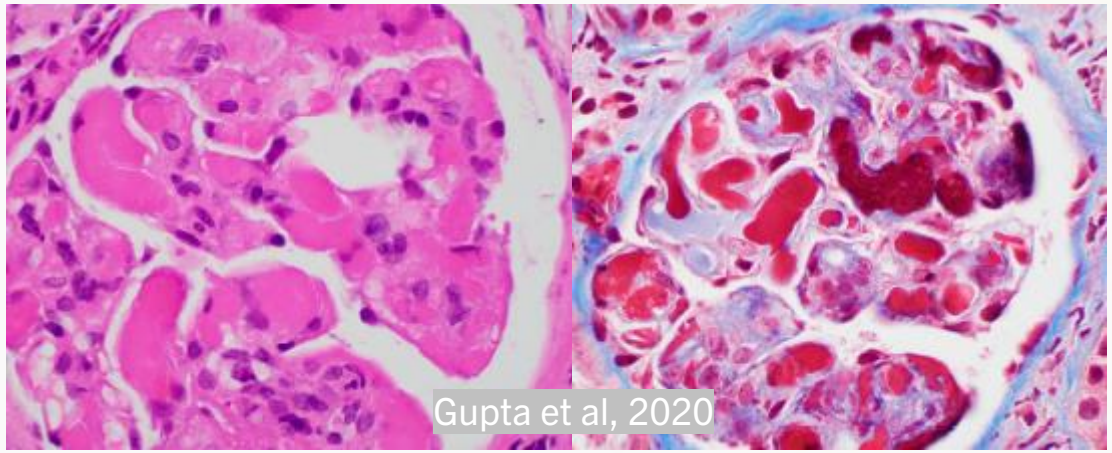
Renal Crystalline Induced Nephropathy

- Kidney biopsy: critical for diagnosis

  In patient with monoclonal gmmopathy : MGUS vs MGRS



Membranoproliferative pattern



Pseudothrombi

Renal Crystalline Induced Nephropathy

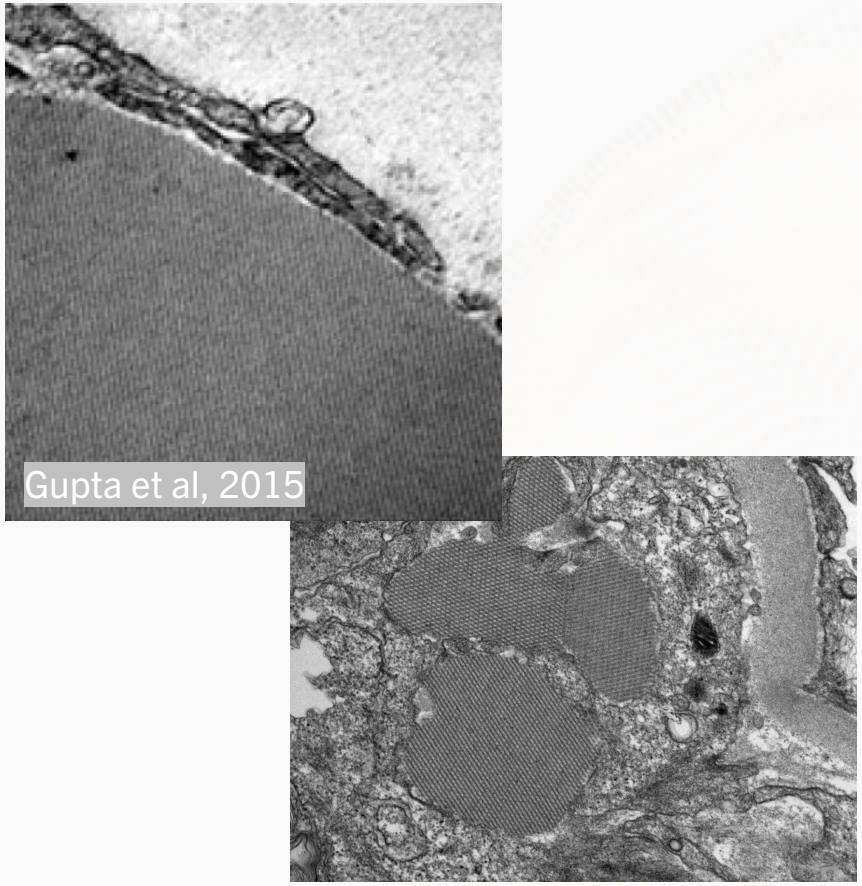
- Kidney biopsy: critical for diagnosis
- Pronase-based antigen retrieval on paraffin-embedded material to unmask antigenic epitopes
  - Conventional immunofluorescence fails to detect monoclonal protein deposits in 40% of cases

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

Leung et al, 2019

Renal Crystalline Induced Nephropathy

- Kidney biopsy: critical for diagnosis
- Pronase-based antigen retrieval on paraffin-embedded material to unmask antigenic epitopes
- Ultrastructural analysis of electron-dense crystalline structures within the kidney microvasculature
- Repeat serum electrophoresis with Immunofixation



TAKE HOME MESSAGES

Renal crystalline induced nephropathy is a rare and underrecognized complication of monoclonal gammopathy

Early recognition of kidney disease caused by monoclonal gammopathy is crucial to guide management

References

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THANK YOU