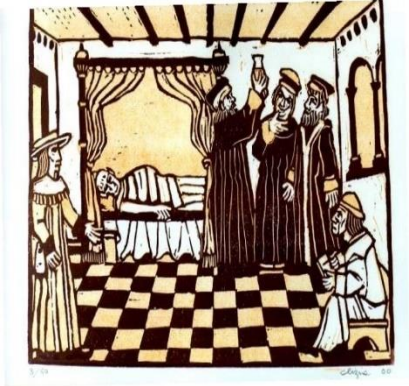

Diagnosis and Treatment of Cryoglobulinemic Vasculitis

Dario Roccatello

Nephrology and Dialysis Unit-CMID
(ERK-net Member)
Center of Research of Nephrology,
Rheumatology, and Rare Diseases
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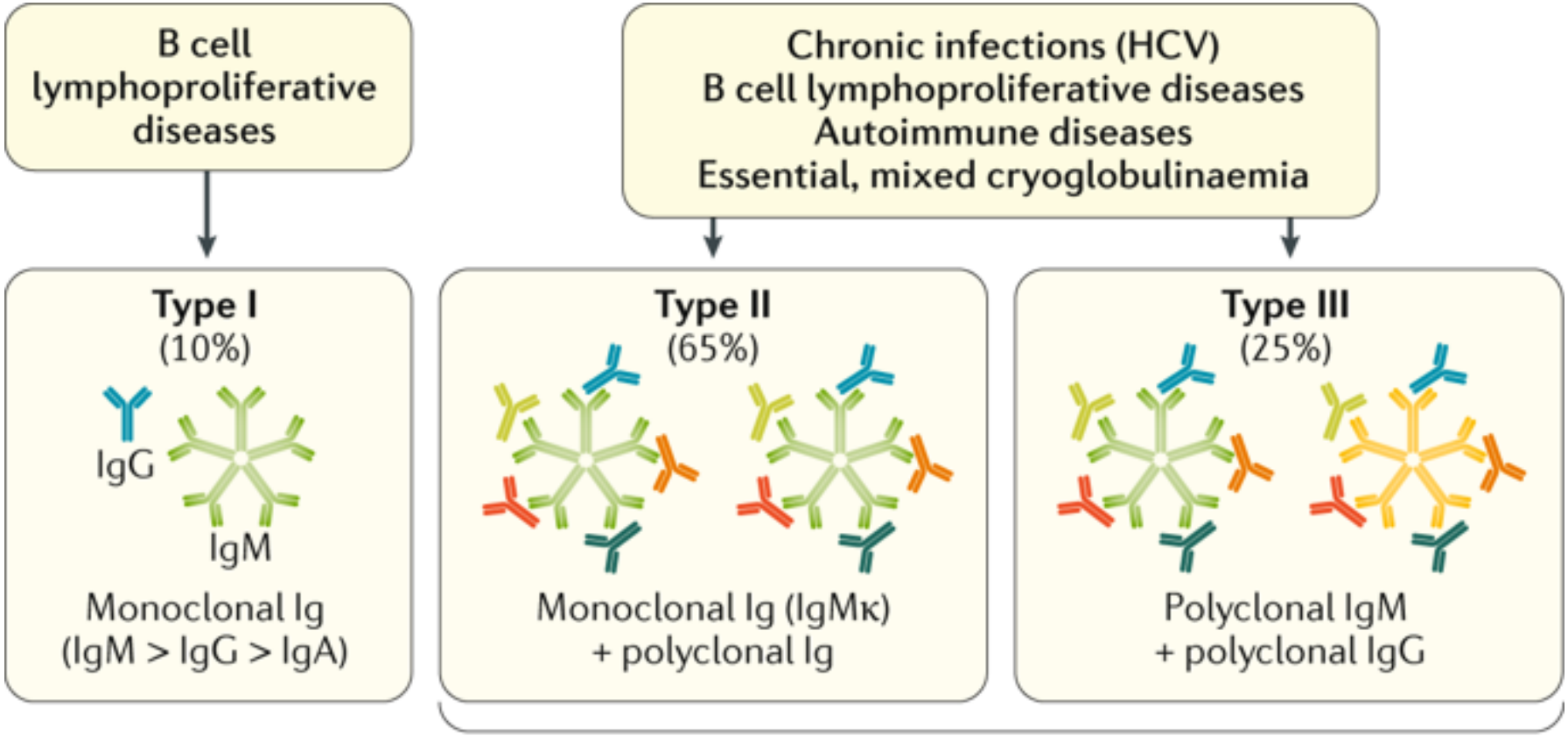
CLASSIFICATION OF CRYOGLOBULINEMIA



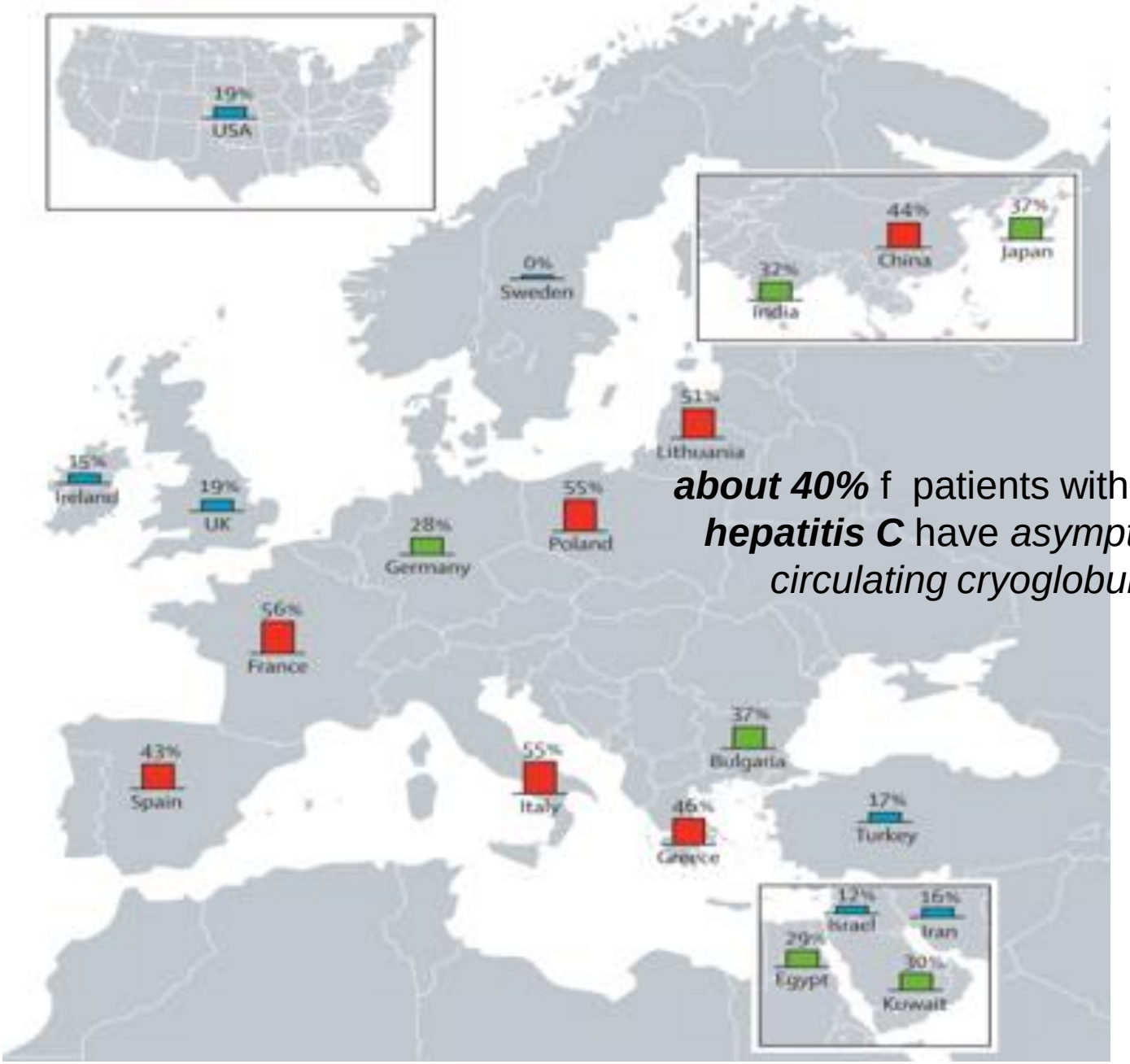
Type I/II MIXED CRYOGLOBULINEMIA

Roccatello, D. et al. (2018) Cryoglobulinaemia Nat. Rev. Dis. Primers

AGENDA

- **Cryoglobulinemic glomerulonephritis**
- Pathogenesis, presentation and prognosis
- Anti-viral therapy
- Standard immunosuppression
- The impact of B cell depletion therapy
- International therapeutic guidelines

Prevalence of cryoglobulinaemia in patients with chronic HCV infection



about 40% f patients with ***chronic hepatitis C*** have *asymptomatic circulating cryoglobulins*

Ramos Casals M, Lancet 2012

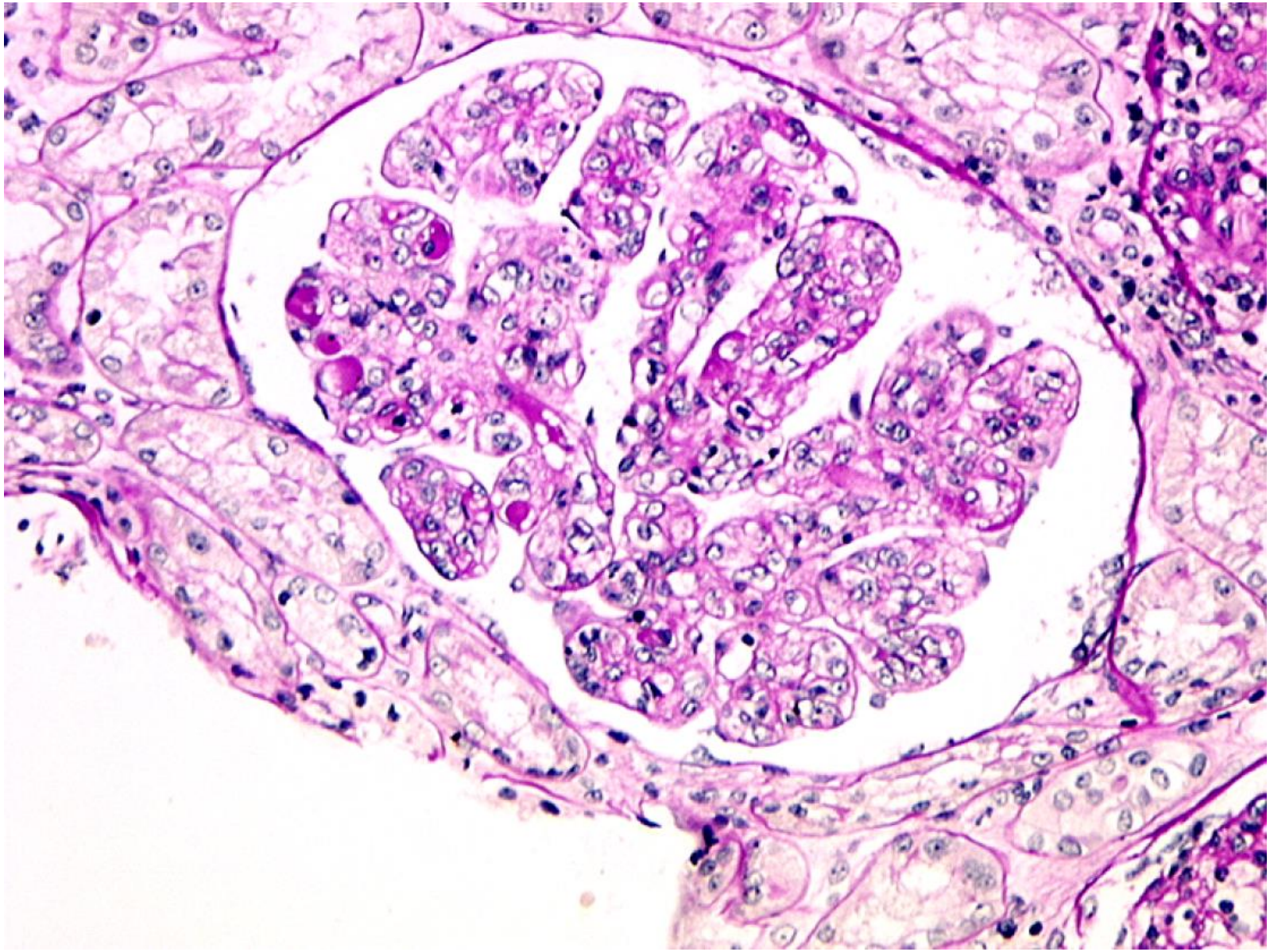
- A ***cryoglobulinemic syndrome*** develops in less than 5 % of cases, and *nephritis* in *0.5% of HCV infected persons*

- ***Genetic background*** probably important

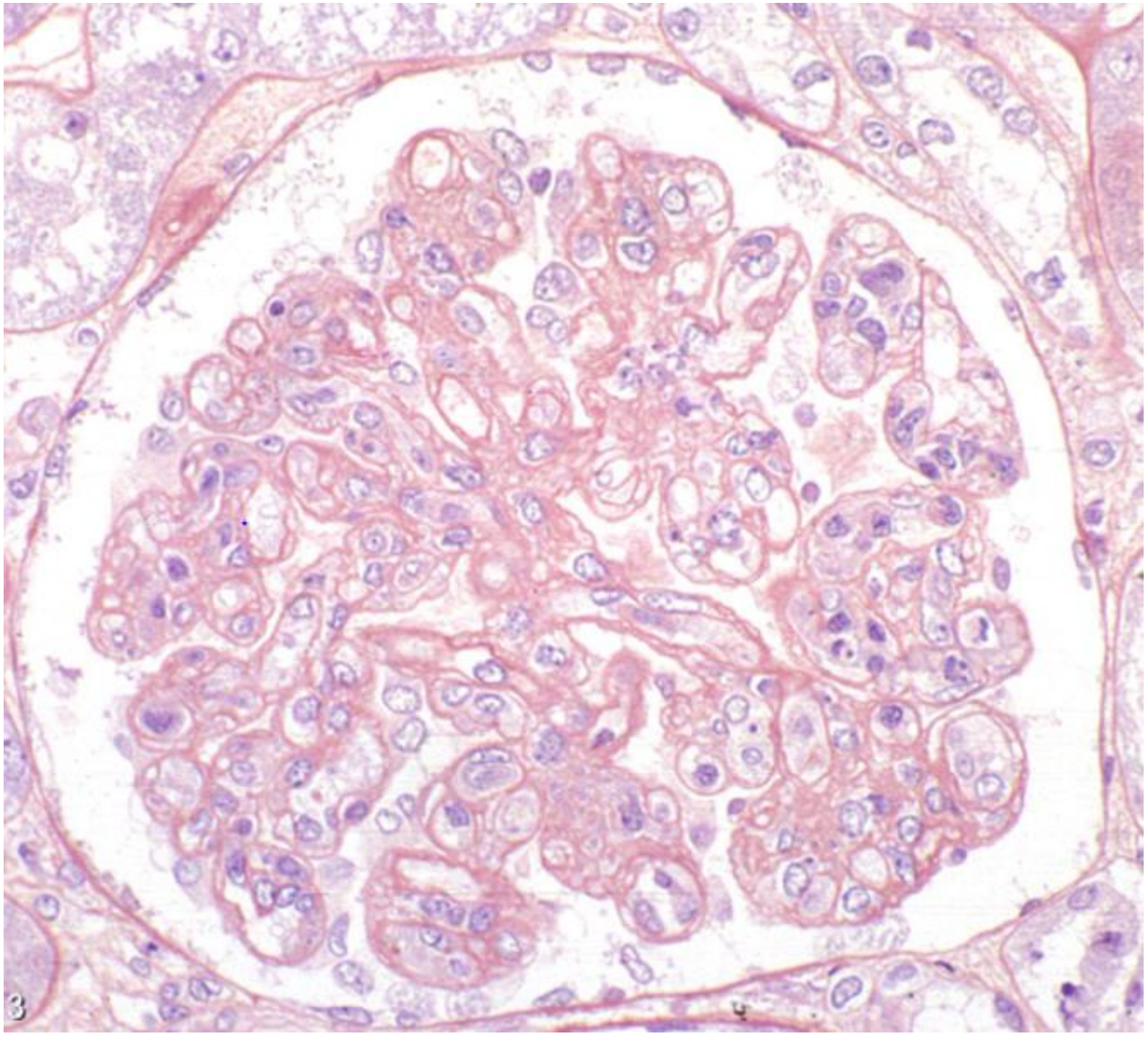
- ***Extrarenal signs*** of MC vasculitis usually ***precede*** the kidney manifestations, but in a minority of cases ***kidney manifestations appear first***

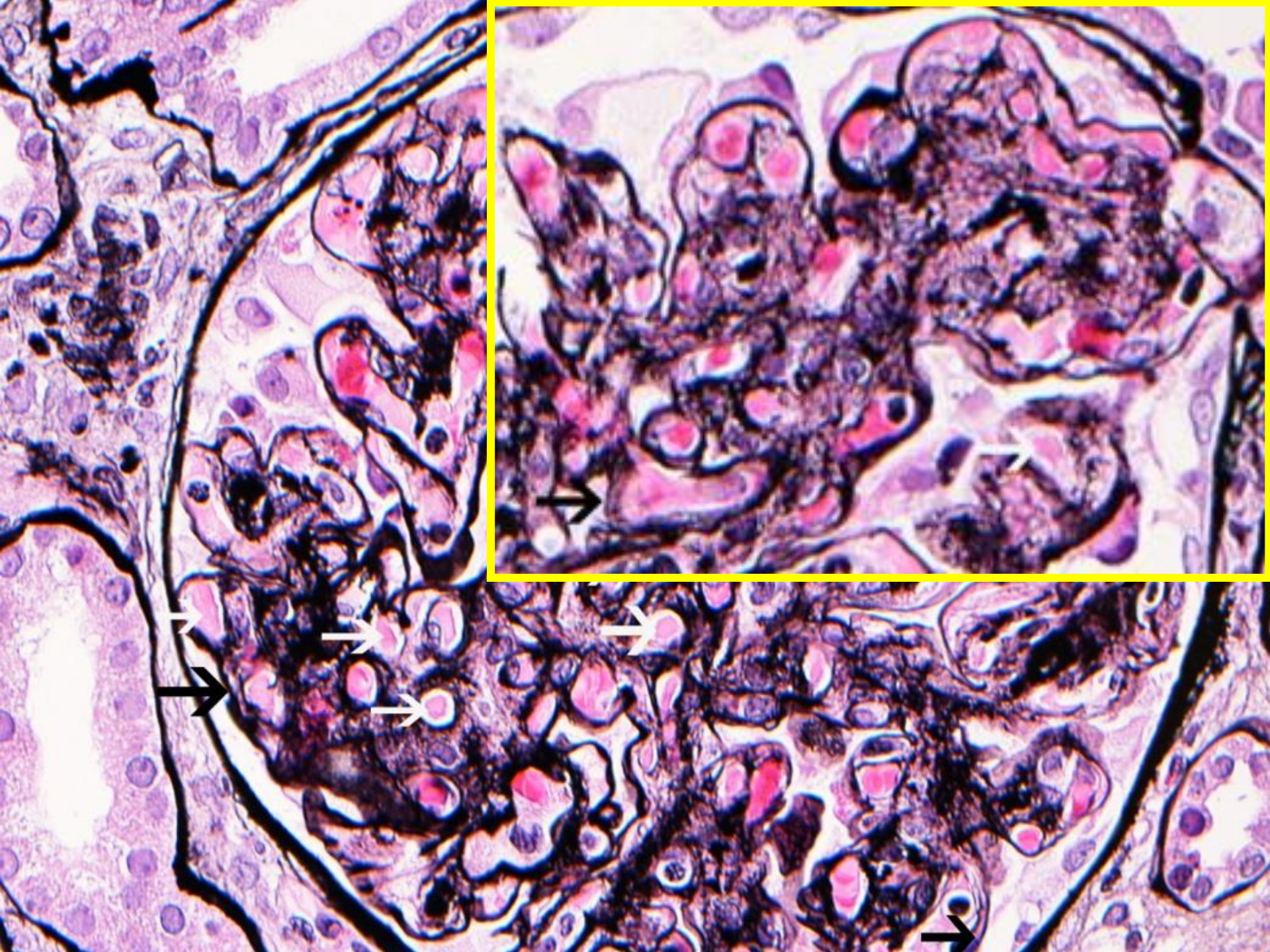
- ***Biopsy mandatory when kidney involvement is supected***

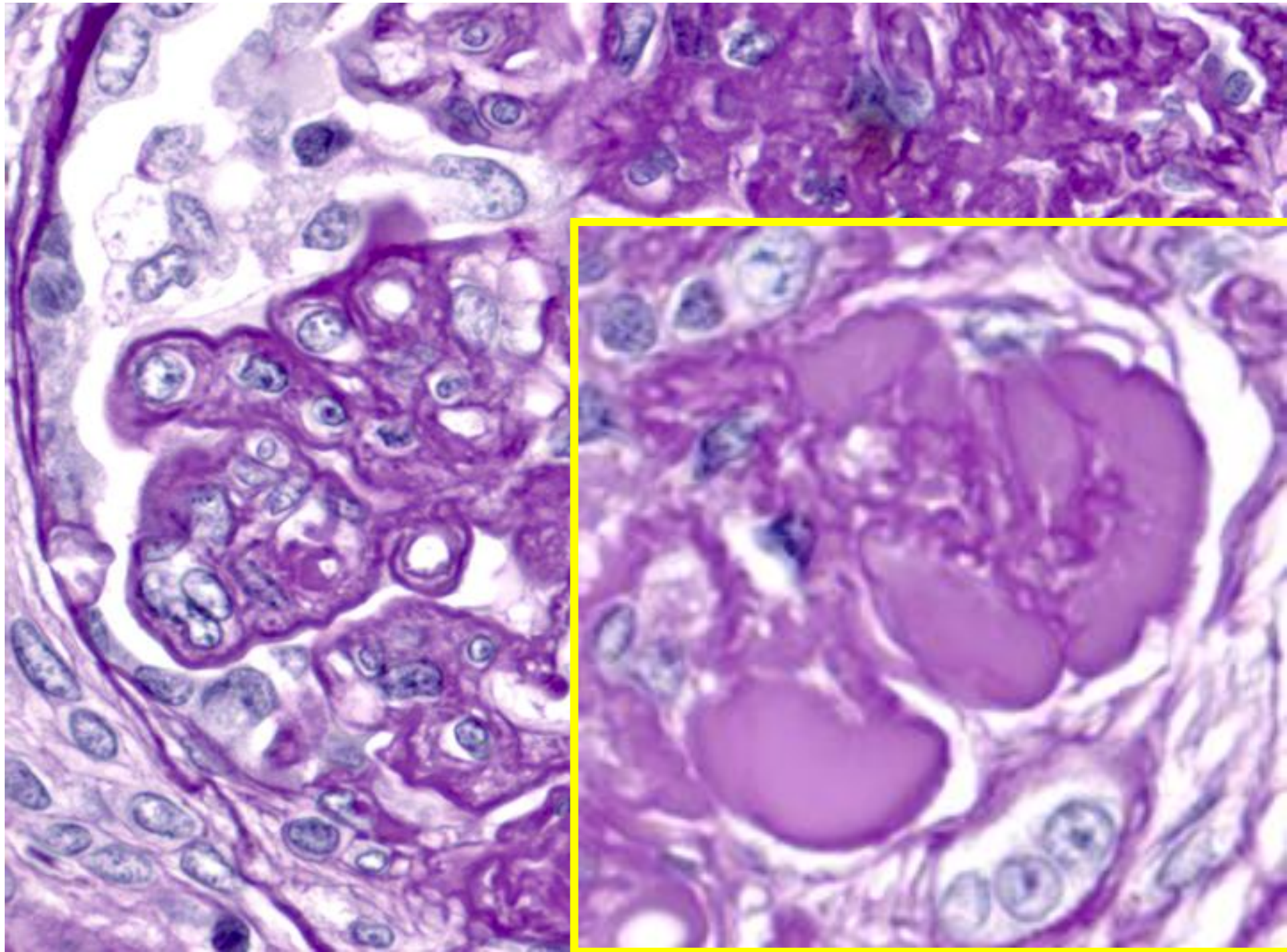
Roccatello and Pani in Core Concepts in Kidney Parenchimal Diseases. Fervenza & Sethi Eds, Springler, 2013

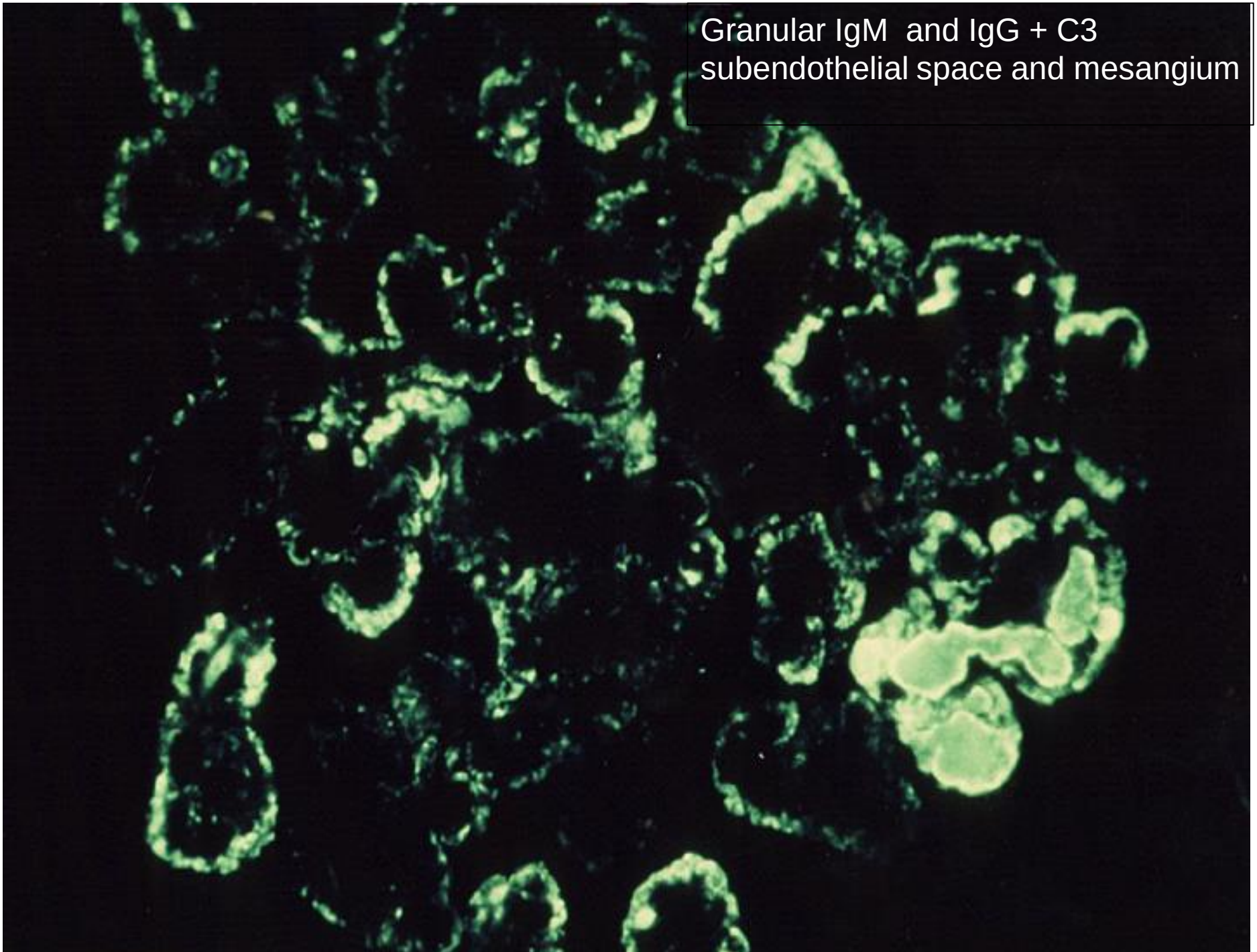


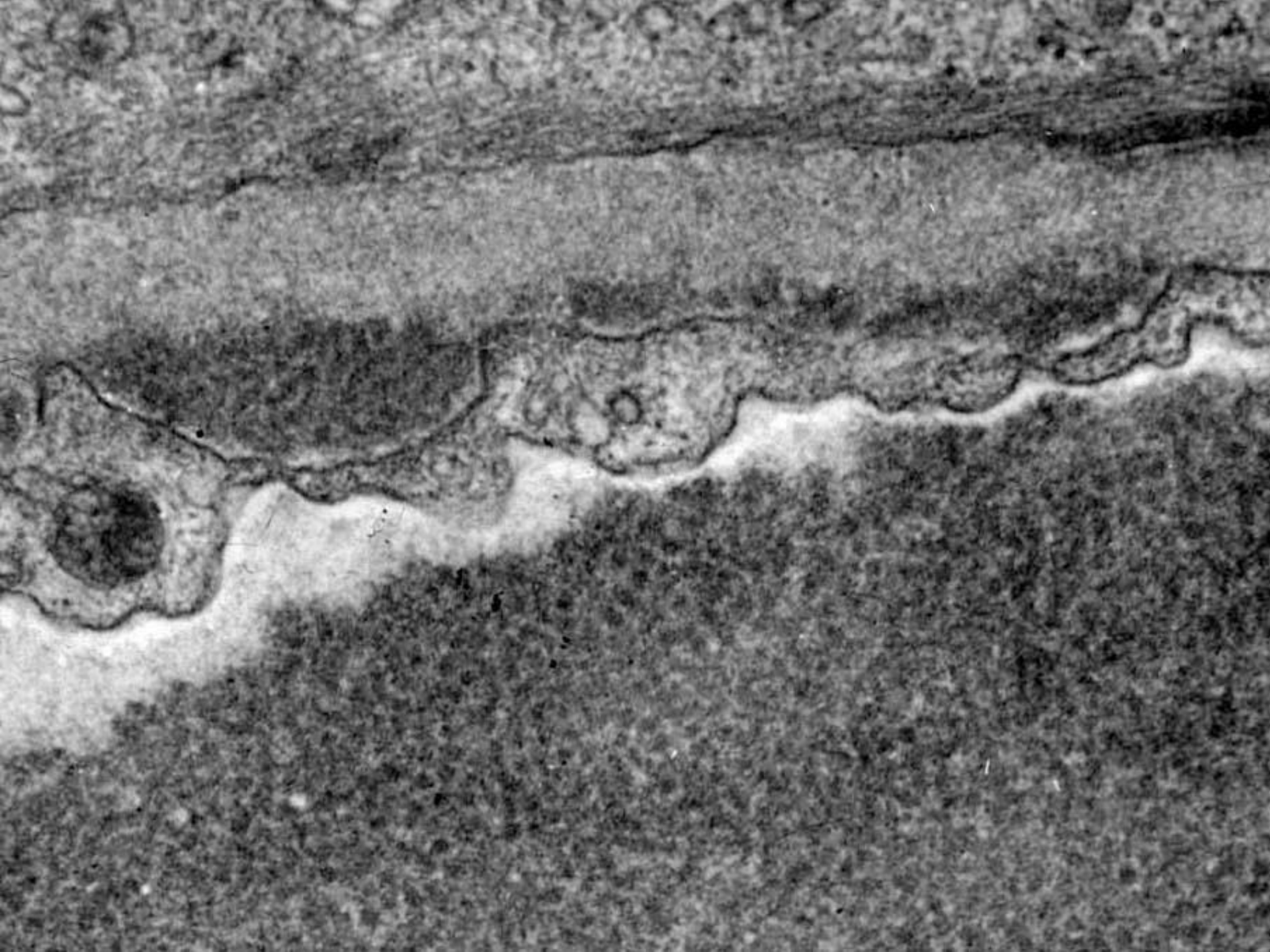
PAS 20x: membrano-proliferative pattern with endocapillary proliferation and deposits in capillary lumina



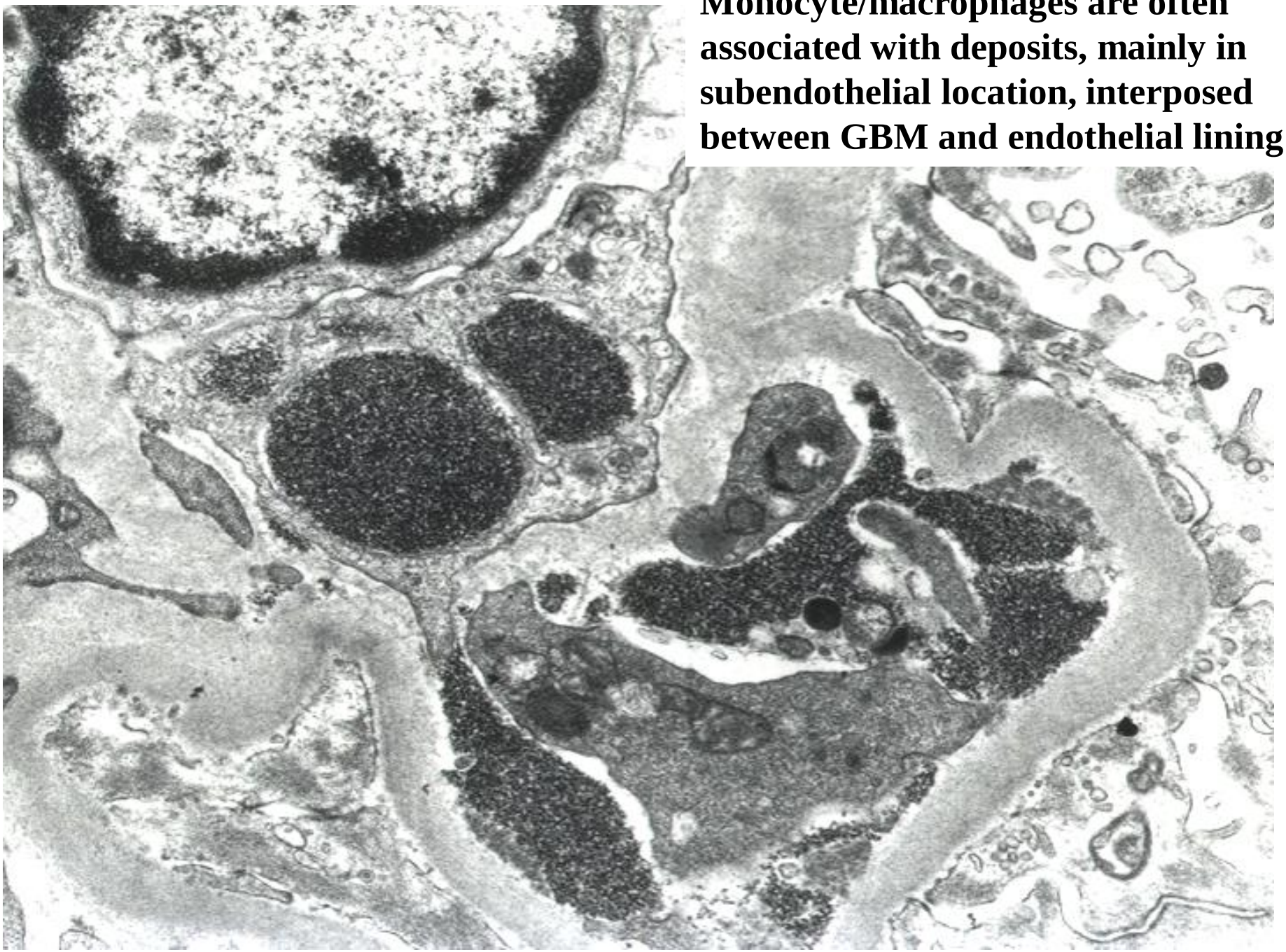


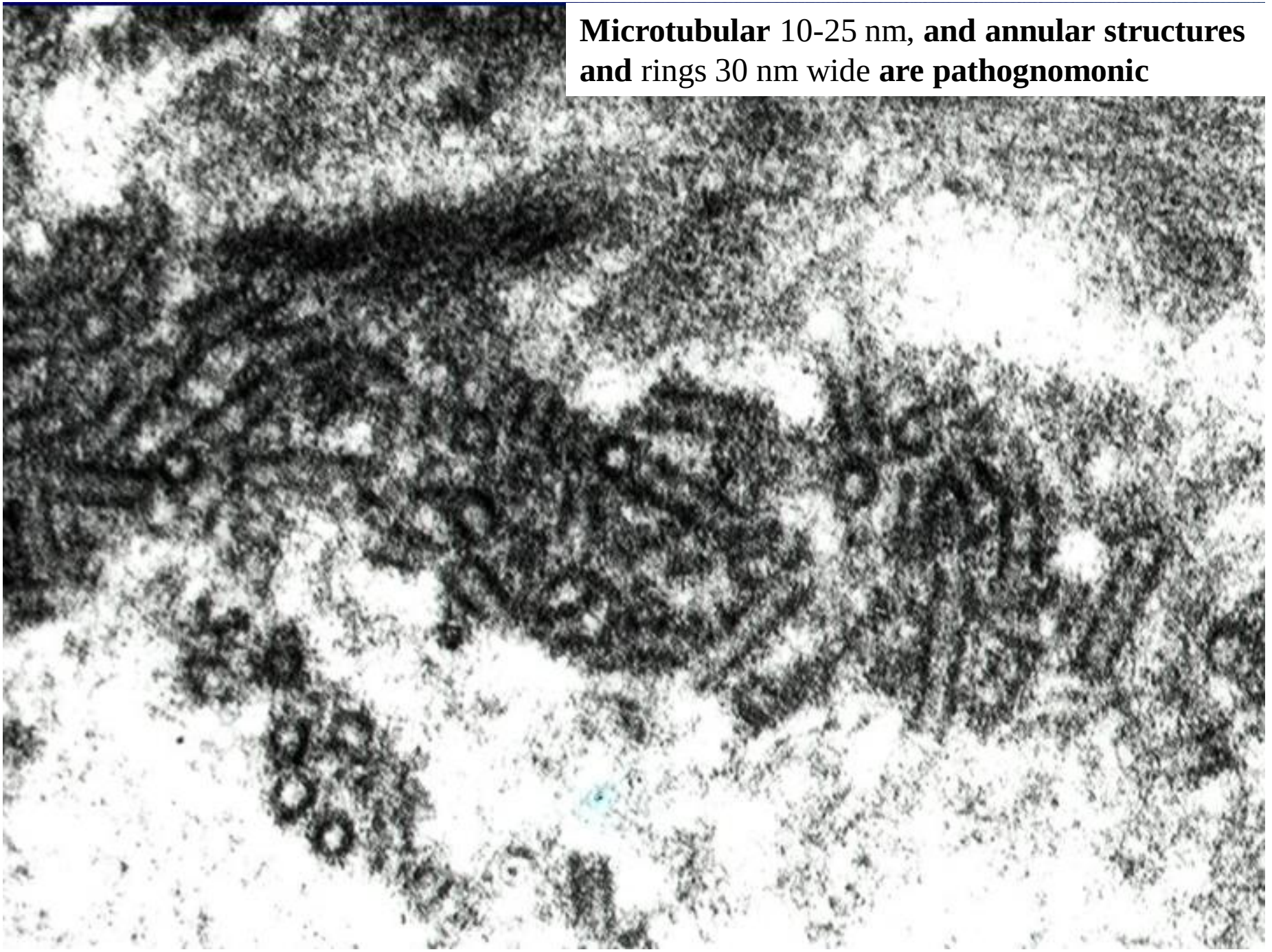



Granular IgM and IgG + C3
subendothelial space and mesangium



Monocyte/macrophages are often associated with deposits, mainly in subendothelial location, interposed between GBM and endothelial lining



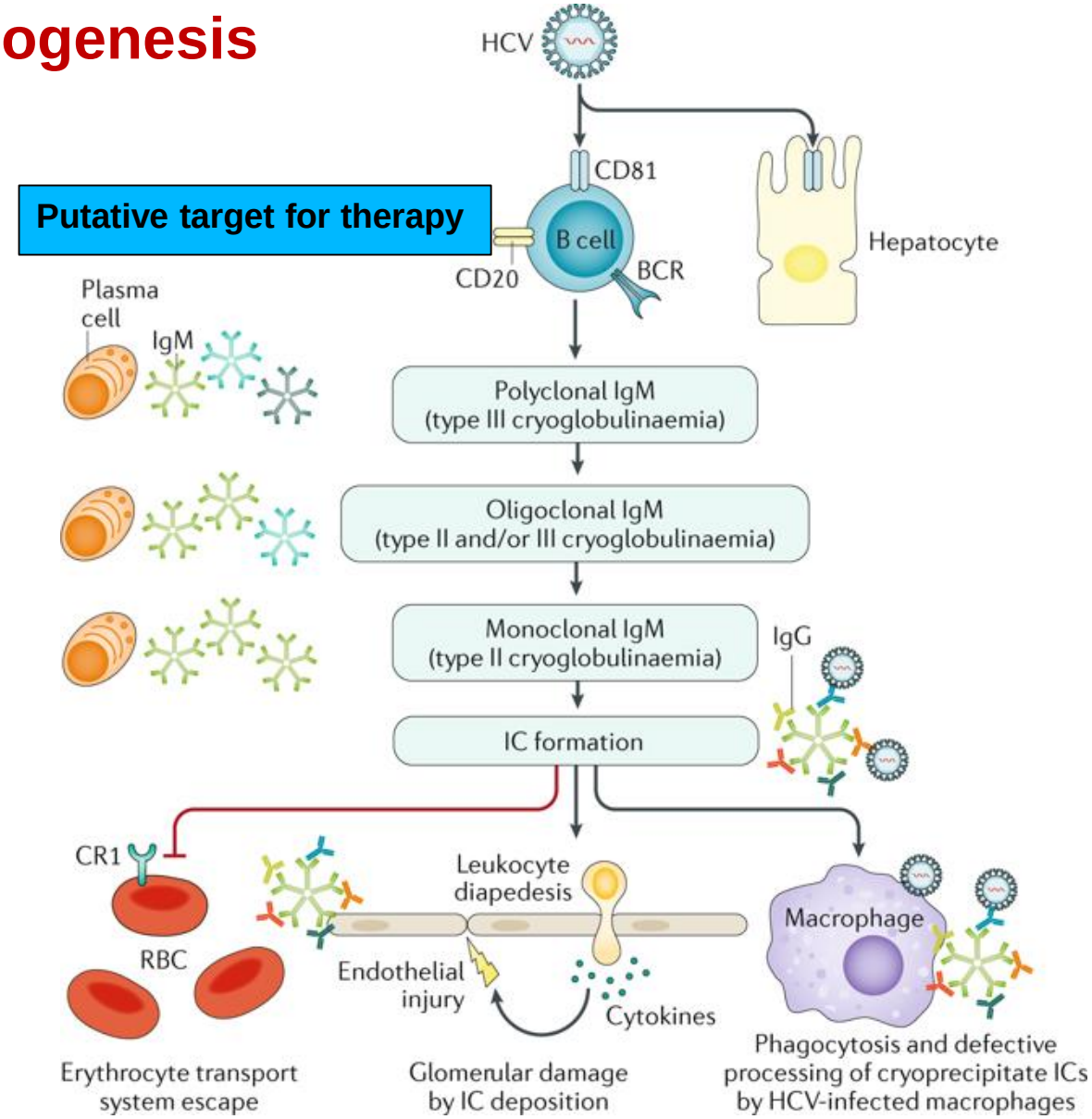


Microtubular 10-25 nm, **and annular structures and** rings 30 nm wide **are pathognomonic**

AGENDA

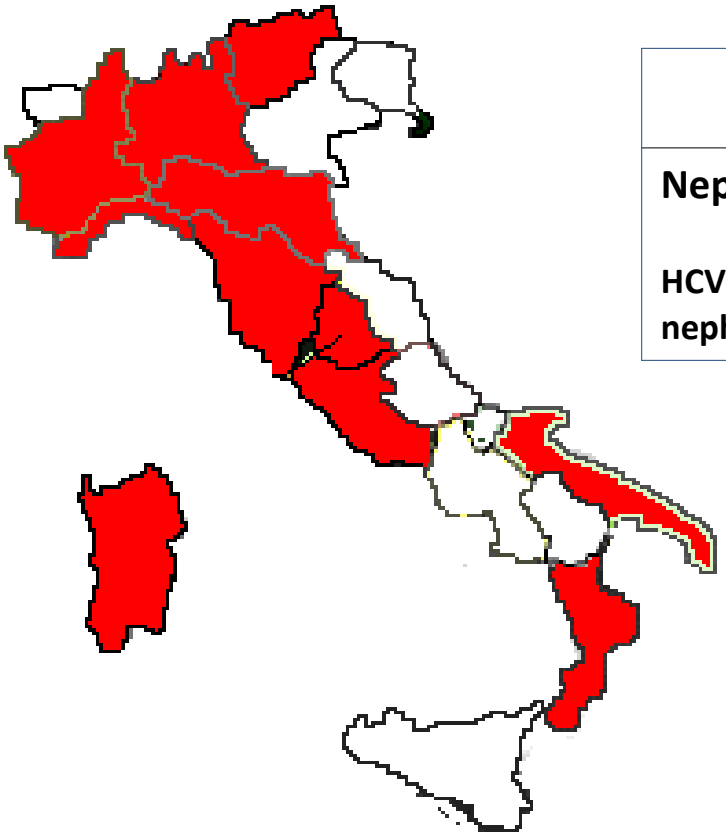
- Cryoglobulinemic glomerulonephritis
- **Pathogenesis, presentation and prognosis**
- Anti-viral therapy
- Standard immunosuppression
- The impact of B cell depletion therapy
- International therapeutic guidelines

Pathogenesis

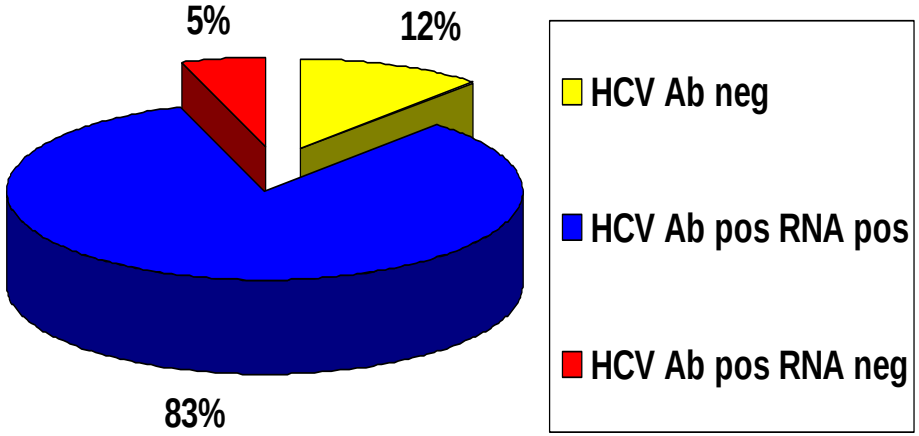


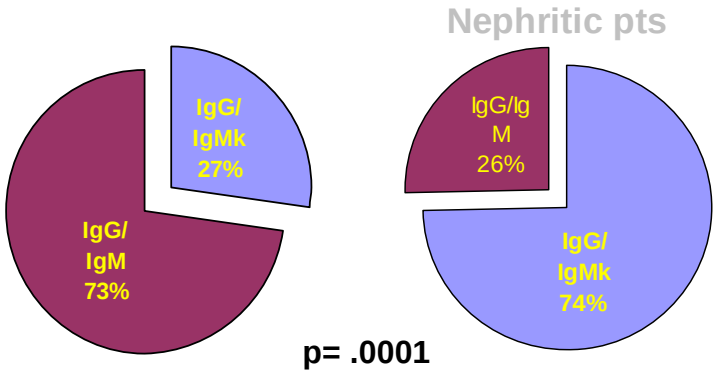
Roccatello et al. Cryoglobulinaemia Nat. Rev. Dis. Primers (2018)

Demographic distribution of MC nephritic patients



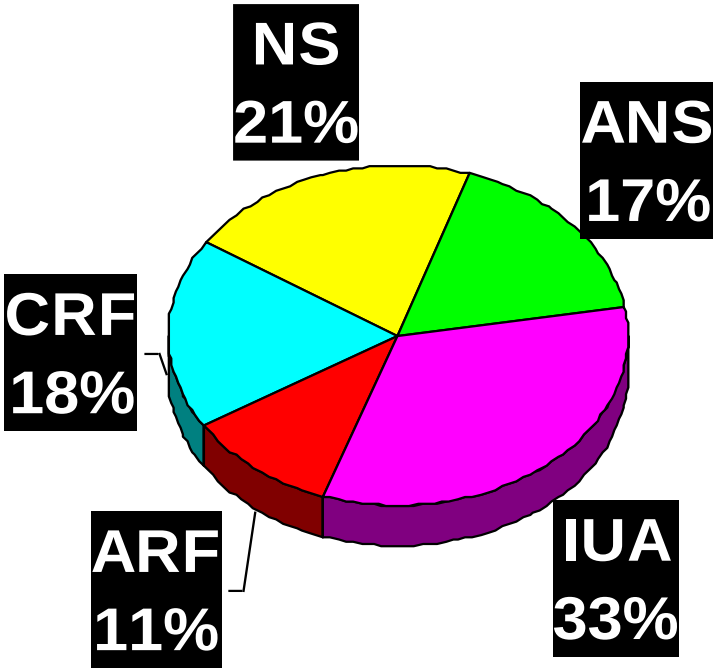
	#	F	M	onset age
Nephritis pts	146	83	63	52.2 ±13
HCV+ve non-nephritis pts	34	20	14	56.7±9.6



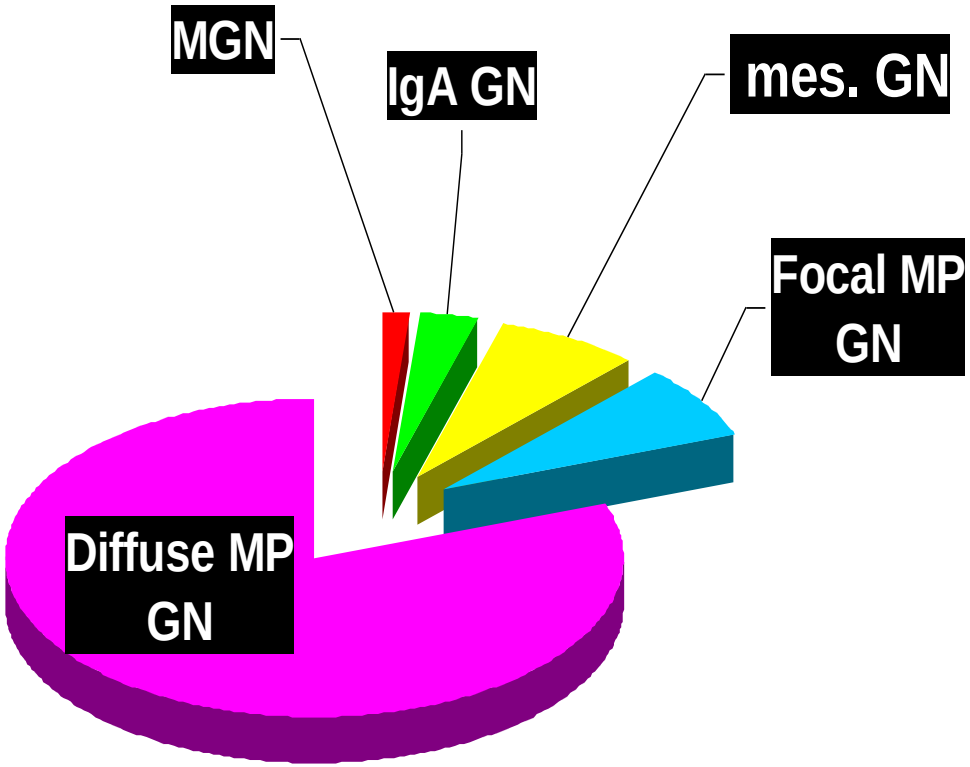


Roccatello & Fornasieri on behalf of the Italian group of immunopathology AJKD, 2007

CLINICAL PRESENTATION



HISTOLOGICAL FEATURES



Roccatello & Fornasieri on behalf of the Italian group of immunopathology AJKD, 2007

EXTRARENAL SYMPTOMS

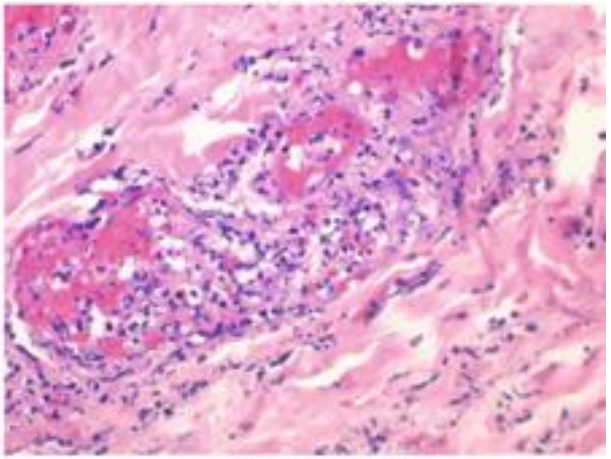
Clinical

Recent purpura

Dyscromic lesions

Serological

Pathological



Serum MCs alone
- Possible preclinical condition with or without RF and/or low C4
- Careful clinical evaluation of possible underlying infectious (HCV or HBV) autoimmune and/or haematological and/or neoplastic disease
- Monitoring without treatment

Mixed cry
Clinical
- Purpura
- Weakne
- Arthralg
- Liver inv
- Renal in
- Skin inv
- Peripher neuropa

Mixed cryoglobulinaemia vasculitis

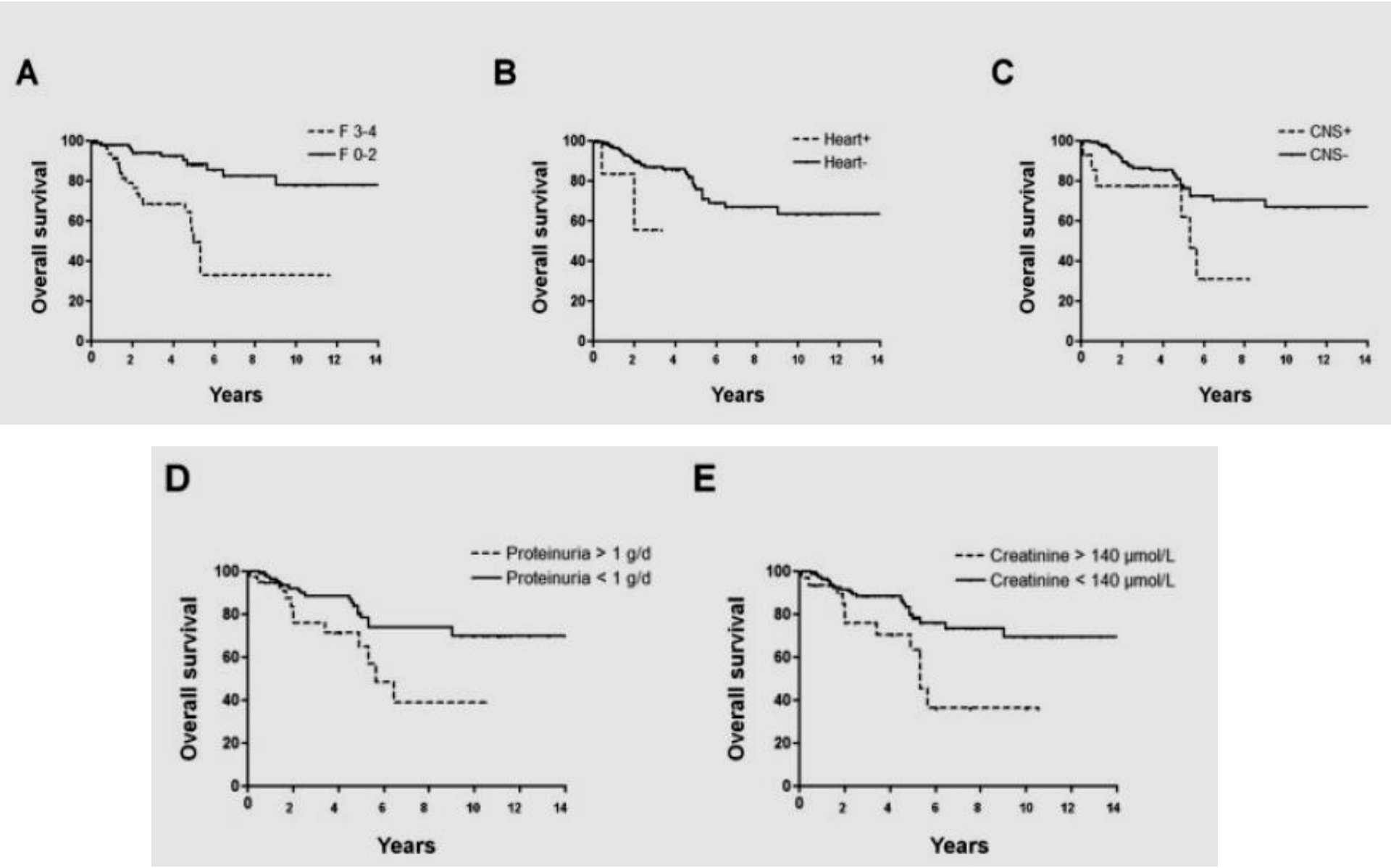
Clinical
- Purpura
- Weakness
- Arthralgias
- Liver involvement
- Renal involvement
- Skin involvement
- Peripheral neuropathy

Serological
- Mixed cryoglobulins
- RF+
- Low C4

Pathological
- Leukocytoclastic vasculitis
- B cell expansion

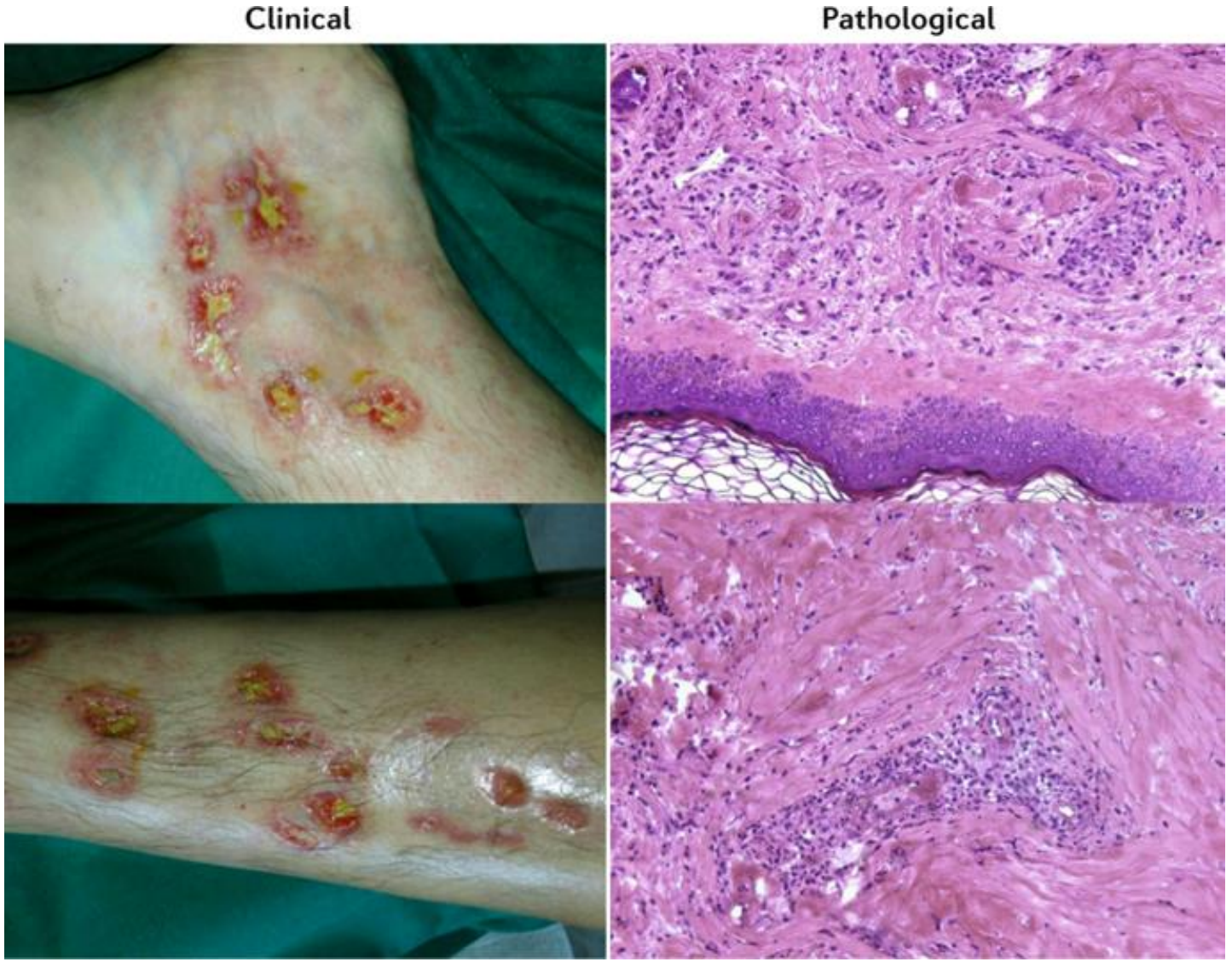
Roccatello, D. et al. (2018) Cryoglobulinae

PROGNOSTIC FACTORS



Terrier B, Arthritis & Rheumatism 2011

Leukocytoclastic vasculitis as a histopathological hallmark

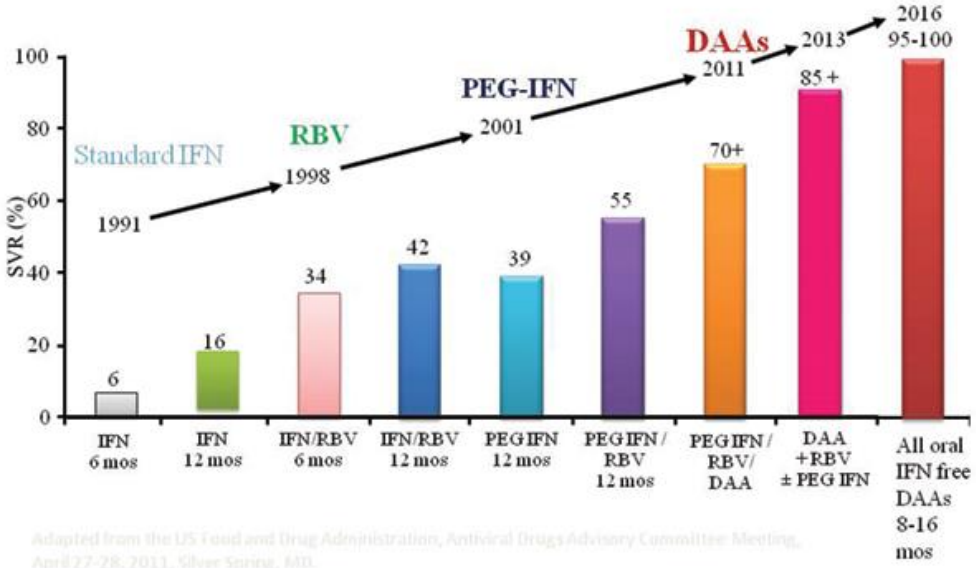


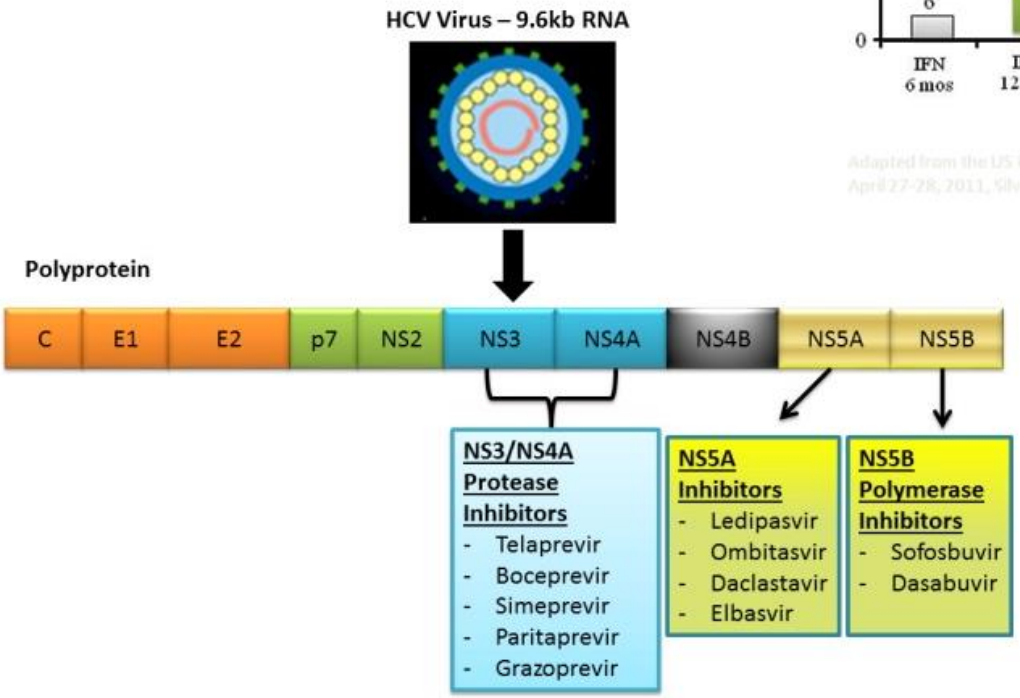
Roccatello, D. et al. (2018) Cryoglobulinaemia
Nat. Rev. Dis. Primers doi.org/10.1038/s41572-018-0009

AGENDA

- Cryoglobulinemic glomerulonephritis
- Pathogenesis, presentation and prognosis
- **Anti-viral therapy**
- Standard immunosuppression
- The impact of B cell depletion therapy
- International therapeutic guidelines

DAAs





The new drugs target the 3 non structural proteins:
- NS3 serine protease and its cofactor NS4A
- NS5A
- NS5B RNA polymerase

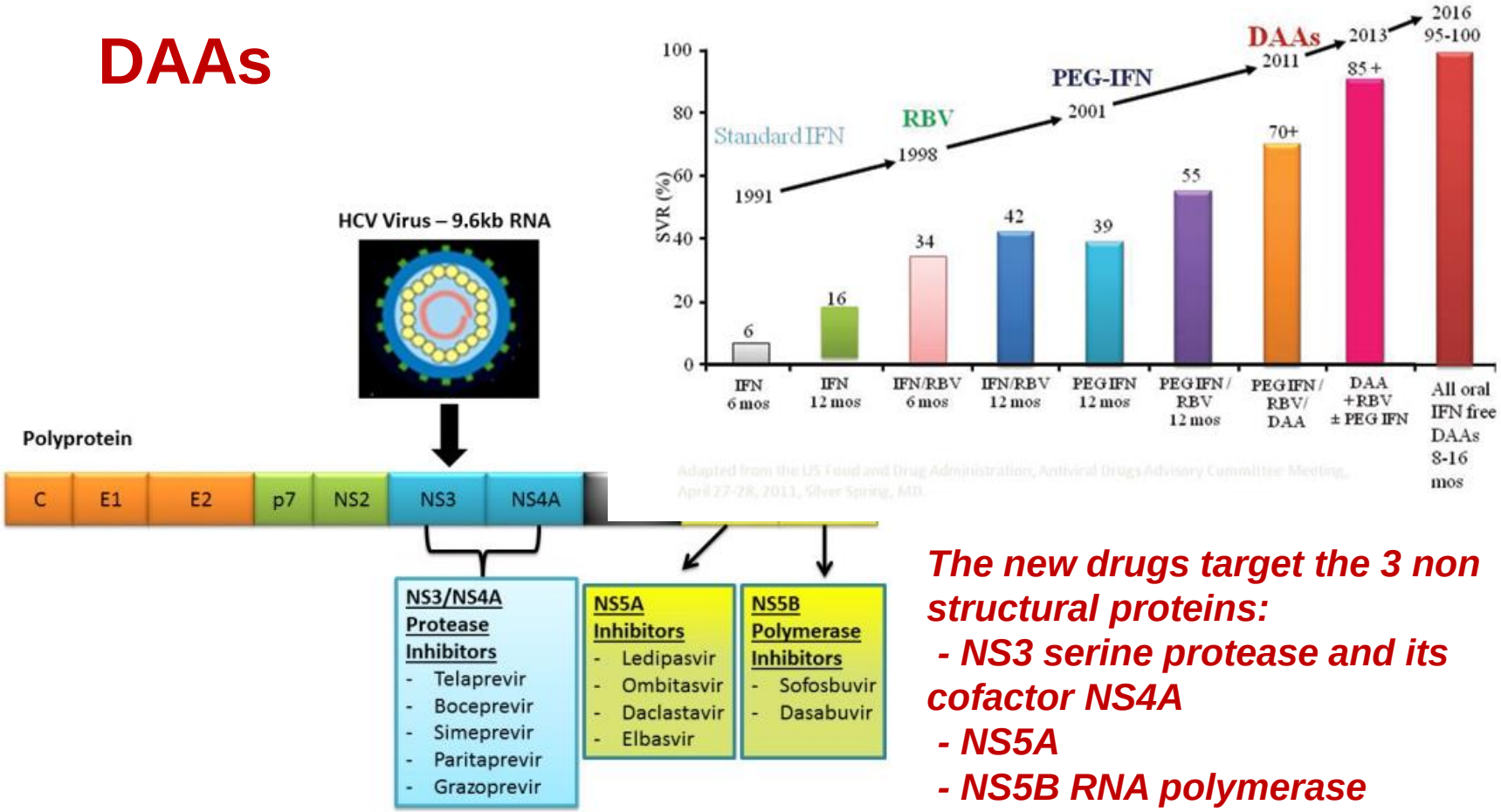
Advances in HCV and cryoglobulinemic vasculitis in the era of DAAs: are we at end of the road?

…several studies have shown positive effects of DAA therapy in pts with MPGN or other HCV related renal manifestations…

Author (year)	N	DAA regimens	RTX (*n*)	SVR (%)	Clinical response (%) at 12 week post-treatment		Complete cryoglobulin reduction (%)
					Complete	Partial	
Saadoun et al. (2016)[91]	24	SOF/RBV × 24 week	4	74	87	-	46
Sise et al. (2016)[97]	12	SOF/SIM (*n* = 8) SOF/RBV (*n* = 4)	4	83	33	33	44 (*n* = 4/9)
Bonacci et al. (2016)[99]	35	3D (*n* = 10) SOF/LDV (*n* = 10) SOF/SIM (*n* = 2) DAC/SIM (*n* = 3) SOF/DAC (*n* = 2) Peg-IFN/DAA (*n* = 5) Others (*n* = 3) Use of RBV (*n* = 24)	0	94	71	14	45
Gragnani et al. (2017)[a 93]	17	3D (*n* = 5) 3D/RBV (*n* = 6) SOF/RBV (*n* = 5) SOF/DAC (*n* = 1)	-	100 (week 8)	30 (week 8)	50 (week 8)	35 (week 8)
Gragnani et al. (2016)[89]	44	SOF/RBV (*n* = 18) SOF/SIM/ ± RBV (*n* = 12) SOF/DAC/±RBV (*n* = 4) SOF/LDV/±RBV (*n* = 10)	2	100	66	27	32
Saadoun et al. (2017)[90]	41	SOF/DAC (*n* = 32) × 12 week SOF/DAC (*n* = 9) × 24 week	2	100	90	10	50
Hegazy et al.[b 137]	35	SOF/RBV (*n* = 13) × 24 week SOF/IFN/RBV (*n* = 8) × 12 week SOF/DAC (*n* = 5) × 12 week SOF/SIM (*n* = 9) × 12 week	-	100	84–100 for each symptom (EOT)	-	-
Emery et al. (2017)[96]	18	DAAs ± IFN	3	89	39	22	29
Sollima et al. (2016)[c 92]	7	3D (*n* = 2) SOF/RBV (*n* = 2) SOF/DAC (*n* = 2) SOF/SIM (*n* = 1)	-	100	0	14	14
Tsuge et al. (2016)[105]	1	DAC/ASU × 24 week	0	100	100	0	0
Obata et al. (2017)[104]	1	DAC/ASU × 24 week	0	100	100	0	0

J Clin and Exp Hepathol, 2017

DAAs



The new drugs target the 3 non structural proteins:
- NS3 serine protease and its cofactor NS4A
- NS5A
- NS5B RNA polymerase

American Association for the Study of Liver Diseases
European Association for the Study of the Liver
both recommend prioritizing DAA treatment in patients with symptomatic MC associated with HCV infection

Advances in HCV and cryoglobulinemic vasculitis in the era of DAAs: are we at end of the road?

…several studies have shown positive effects of DAA therapy in pts with MPGN or other HCV related renal manifestations…

Renal manifestations published in non-nephrologic Journals

- **Gragnani, 4 pts *Hepatology, 2016***
- **Sise, 7 pts *Hepatology, 2016***
- **Bonacci, 7 pts *Clin Gastroenterol Hepatol, 2017***
- **Obata, 1 pt *CEN Case Report, 2017***
- **Tsuge, 1 pt *Hepatol Research,2016***

Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia

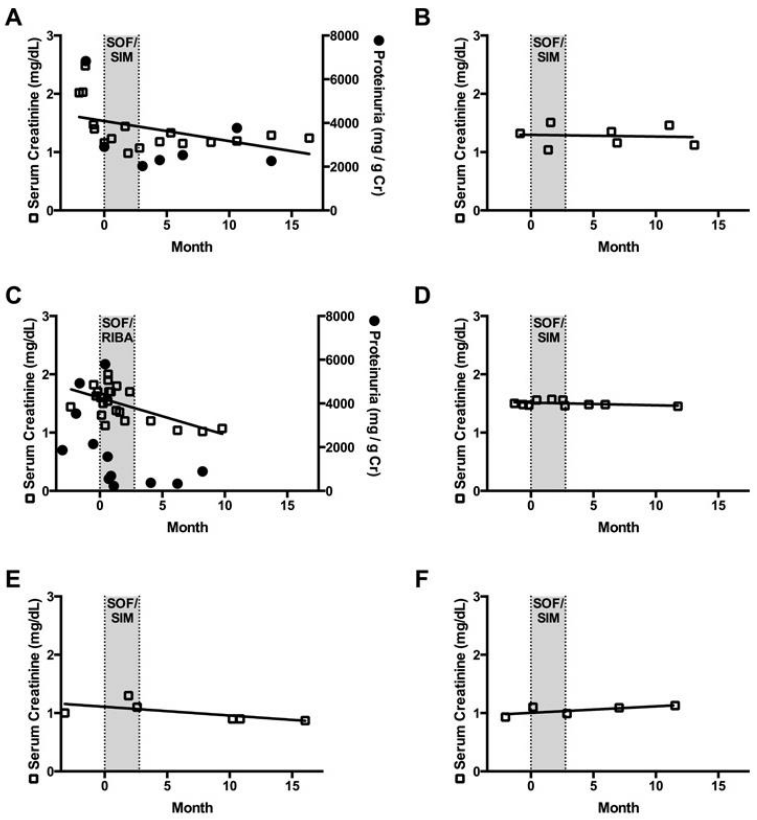
Gragnani et al, Hepathology 2016

Main clinical manifestations :

Palpable purpura (73%),
arthralgia (59%),
weakness (77%),
peripheral neuropathy (63%),
Raynaud's phenomenon (32%),
Sicca syndrome (41%),
Skin ulcers (14%)

Renal involvement (9%),
- **1 had a renal biopsy showing membranoproliferative GN**
- **1 had a nephrotic syndrome**
- **2 had reduced GFR**

Treatment of Hepatitis C Virus-Associated Mixed Cryoglobulinemia with Sofosbuvir-Based Direct-Acting Antiviral Agents



sCr (hollow squares) and proteinuria (dark circles, panels A,C,G) values obtained 3 months prior to direct-acting antiviral therapy initiation, through treatment period (gray) and through last follow-up visit. Patients 1–6 (panels A-F) achieved SVR12. Patient 7 (Panel G) relapsed four weeks after completing therapy.

7/12 reduction in proteinuria/eGFR improvement

BUT

- **Only 2 pts had a clear sCr improvement (1 given RTX and 1 with only a clinical diagnosis)**
- **Changes were negligible in 4 pts,**
- **sCr increased over time in the remaining pt.**
  - **The only pt who had NS received also RTX.**
  - **Another pt with proteinuria from 1,574 to 800 mg/gCr was concomitantly given ustekinumab.**
  - **Proteinuria decreased from 2 to 0.4 mg/gCr in 1 pt who did not undergo renal biopsy.**
  - **Of the remaining 4 pts, proteinuria was negative in 1, not determined in 1 and only determined by urinalysis (1 and 3+ in 2)**

Sise, *Hepatology, 2016*

Cacoub et al Clin Gastroenterol Hepatol 2018
Long-Term Efficacy of Interferon-Free Antiviral Treatment Regimens in Patients With HCV CryoglobulinemiaVasculitis.

Prospective international multicenter study on 148 patients with HCV-CryoVas

Cryoglobulinemia……...132/148
Previous GS, RTX, PE, IS…….. 62/148
Low C4…….. 61/148
Renal involvement……25/148

As in all trials using DAAs in CV, a half of patients remained positive for cryoglobulins.

A severe form of CryoVas and peripheral neuropathy were associated with a lack of response of HCV-CryoVas to DAA

Clinical case #1

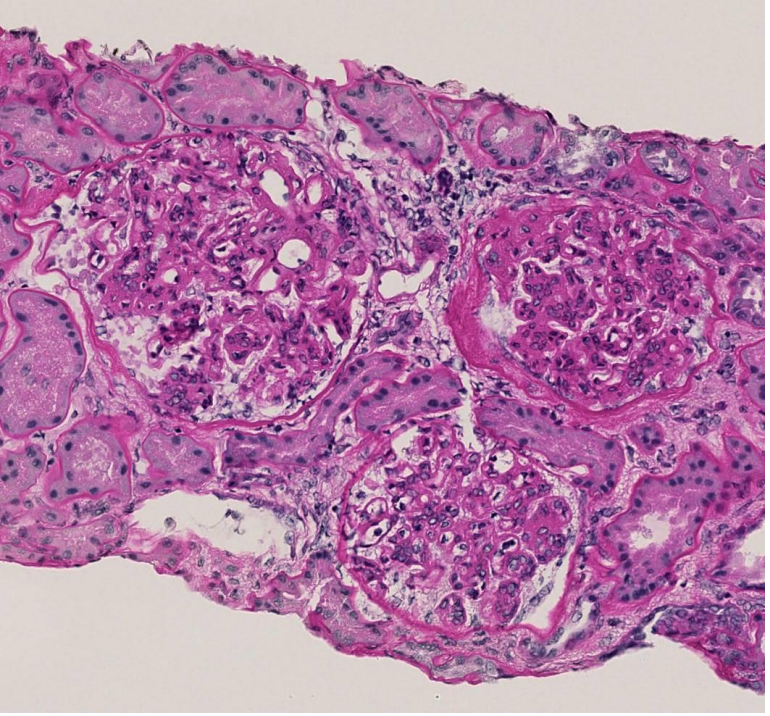
55-year-old man

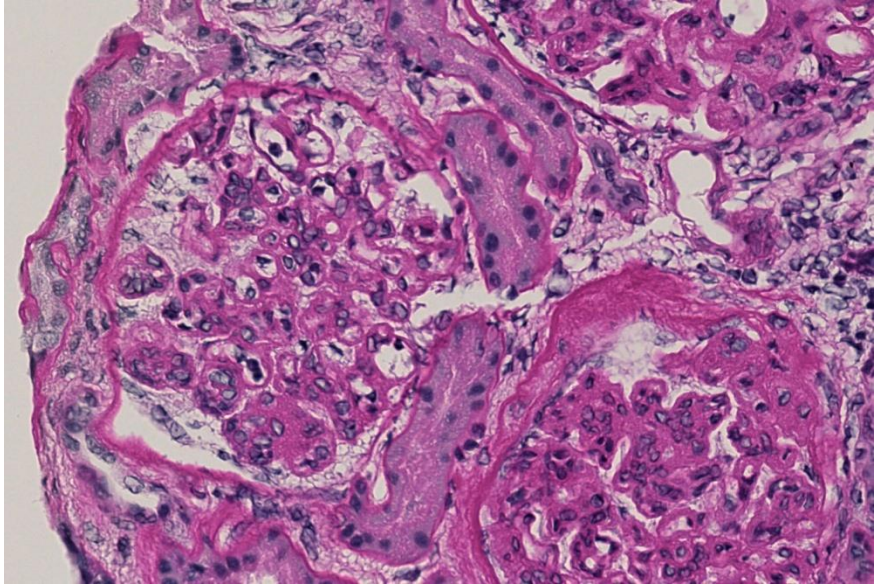
January 2015

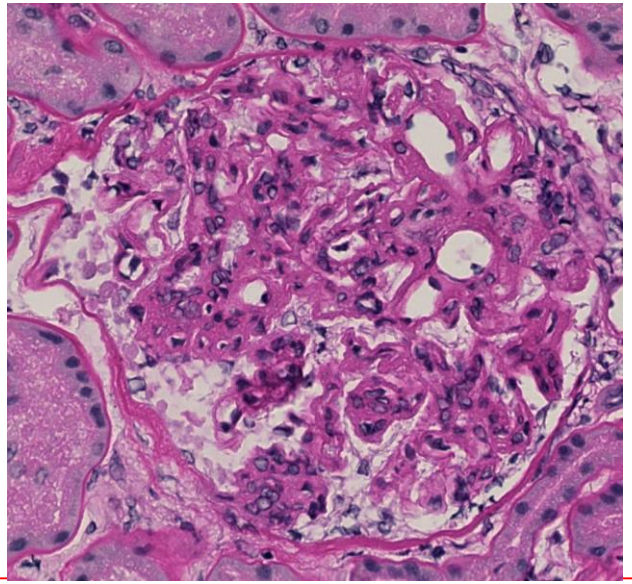
- **Proteinuria 4.5 g/day**
- **sCrs 1.7 mg/dl**
- **Microscopic haematuria ++**
- **C3: 75 mg/dl, C4: 5 mg/dl**
- **IgM 484 mg/dl**

- **HCV RNA: 539265 UI/ml**
- **Genotype 4**
- **Cryocrit 0.5%**
- **Cryoglobulins IgG and IgM polyclonal**
- **RF activity 122**

Renal Biopsy







Light microscopy: mesangial proliferation and endocapillary hypercellularity with segmental distribution

IF: IgM +++ C3 +++, IgG ++, C1q ++, IgA + intramembranous /subendothelial

➢ Treatment with *Ribavirin* and *Sofosbuvir* for six months
(February 2015-August 2015)

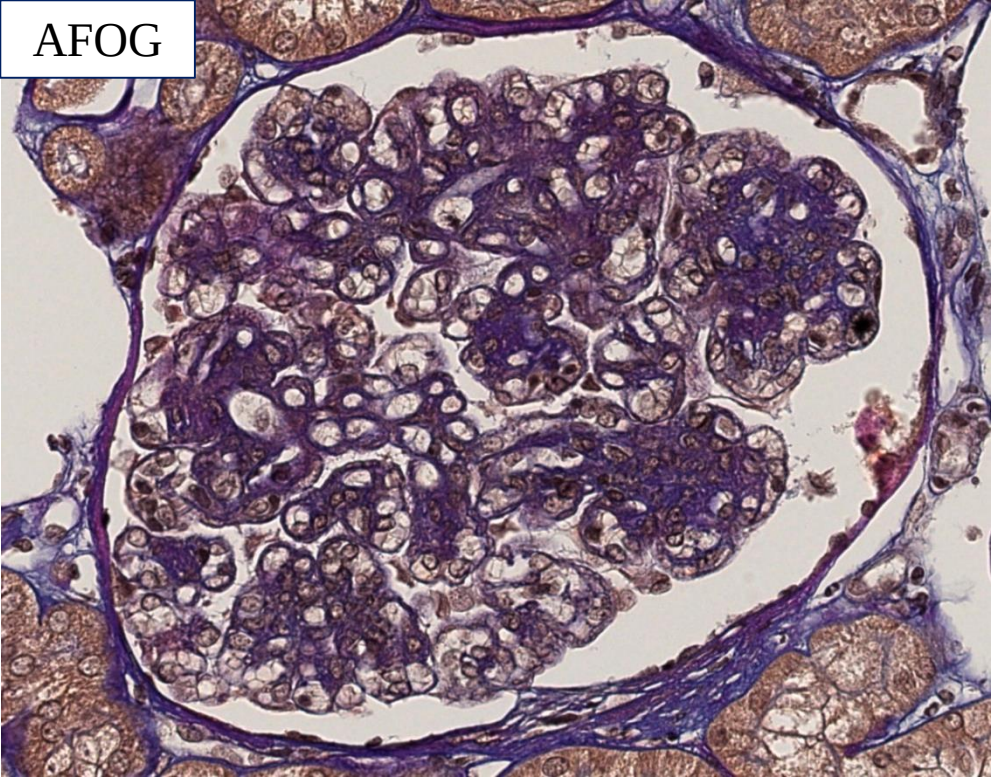
At the end of the therapy
(August 2015):

- **HCV RNA negative**
- **sCr 2 mg/dl**
- **Proteinuria 3.4 g/day**
- **Microscopic haematuria**

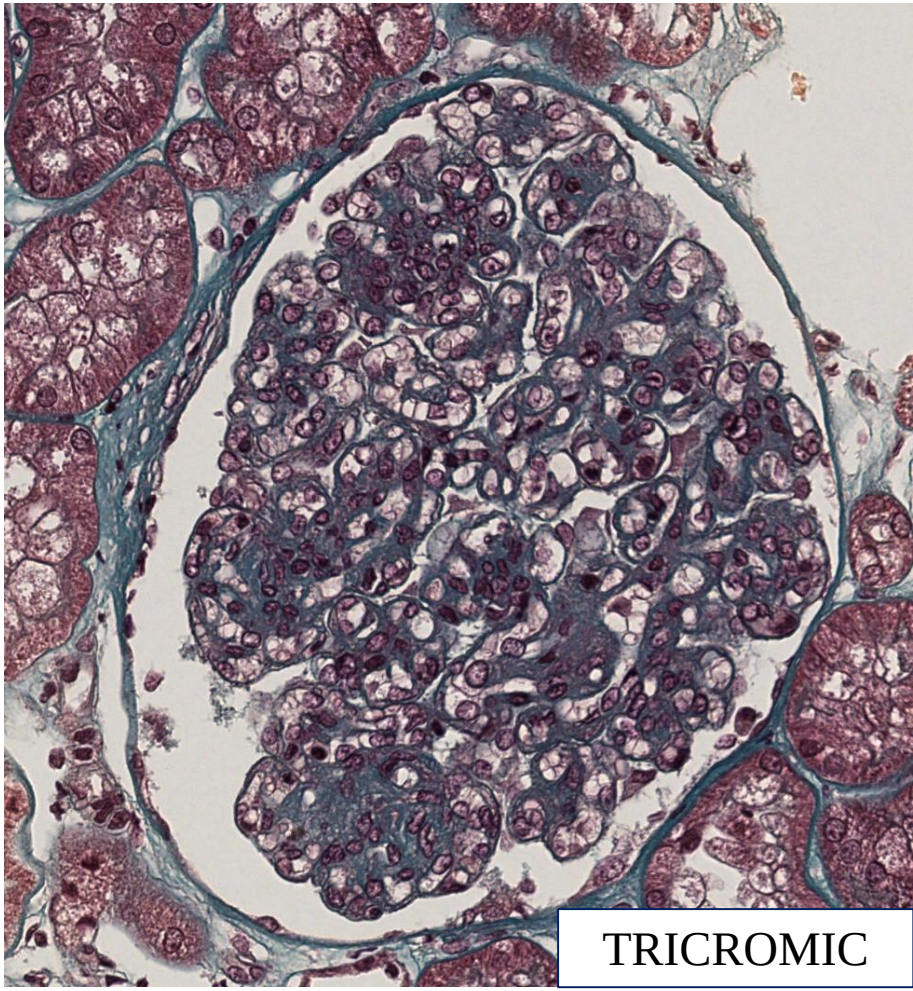
After 18 months
(February 2017):

- **HCV RNA negative**
- **sCr 1.9 mg/dl**
- **Proteinuria 5.7 g/day**
- **Microscopic haematuria**

AFOG



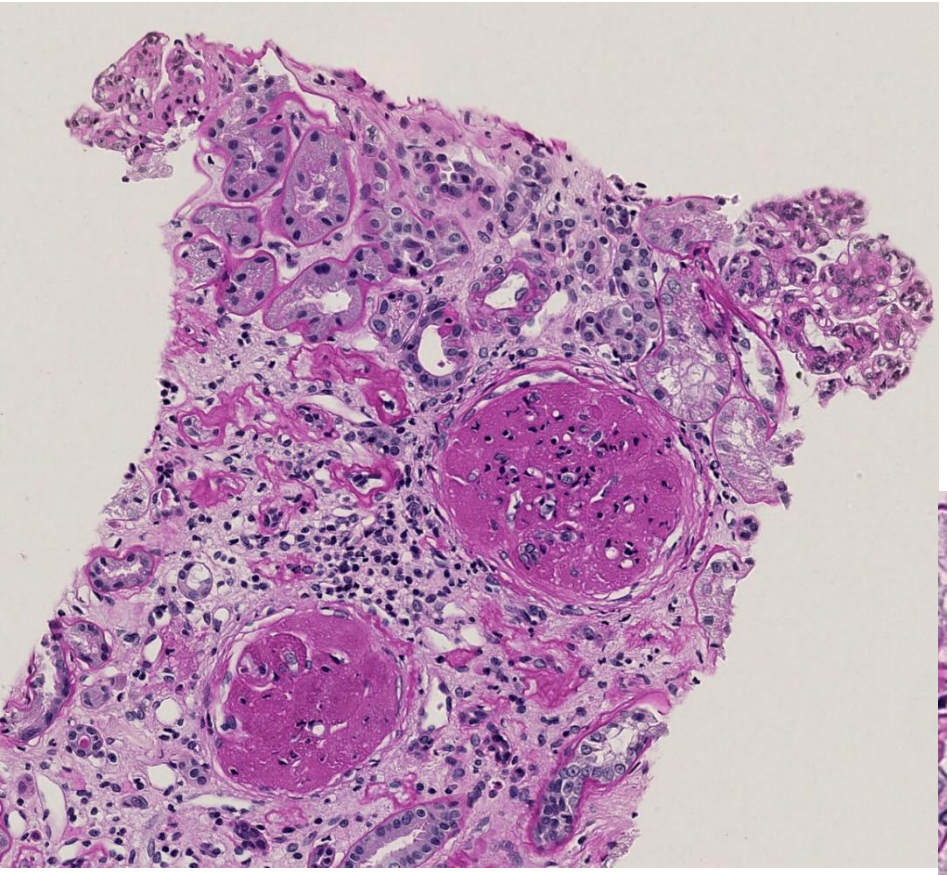
2nd Renal Biopsy



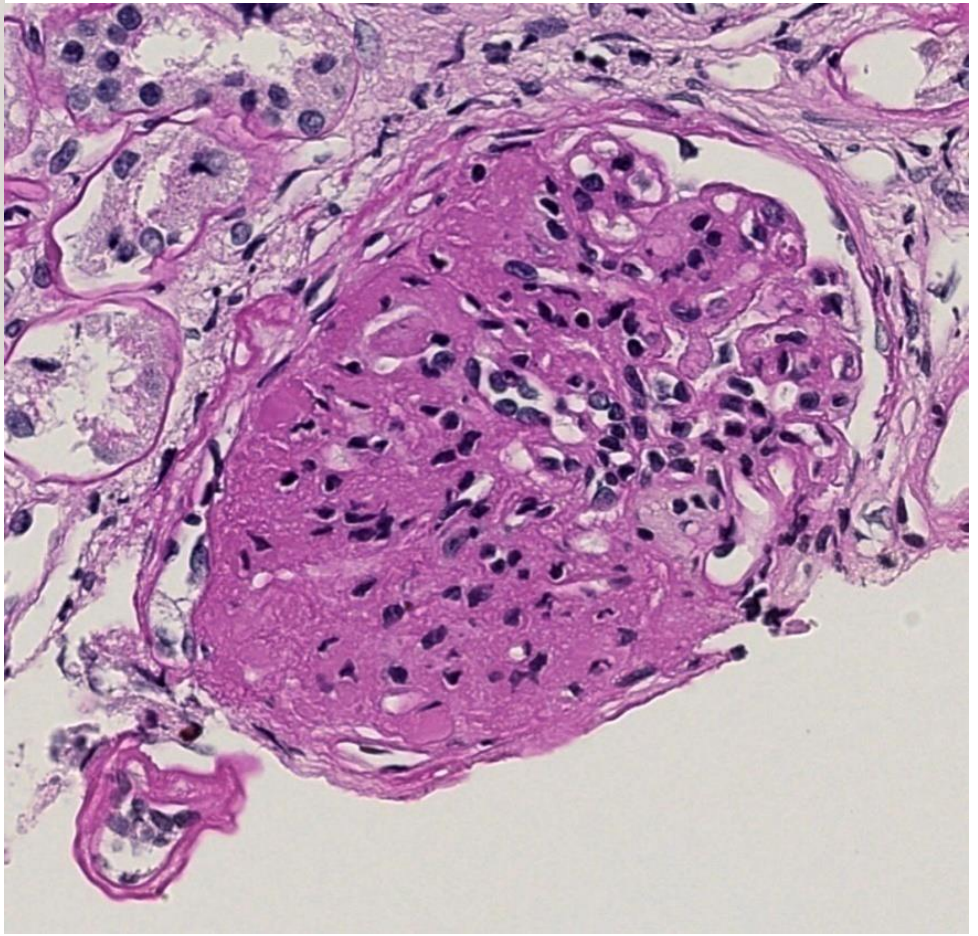
TRICROMIC

Immunofluorescence:

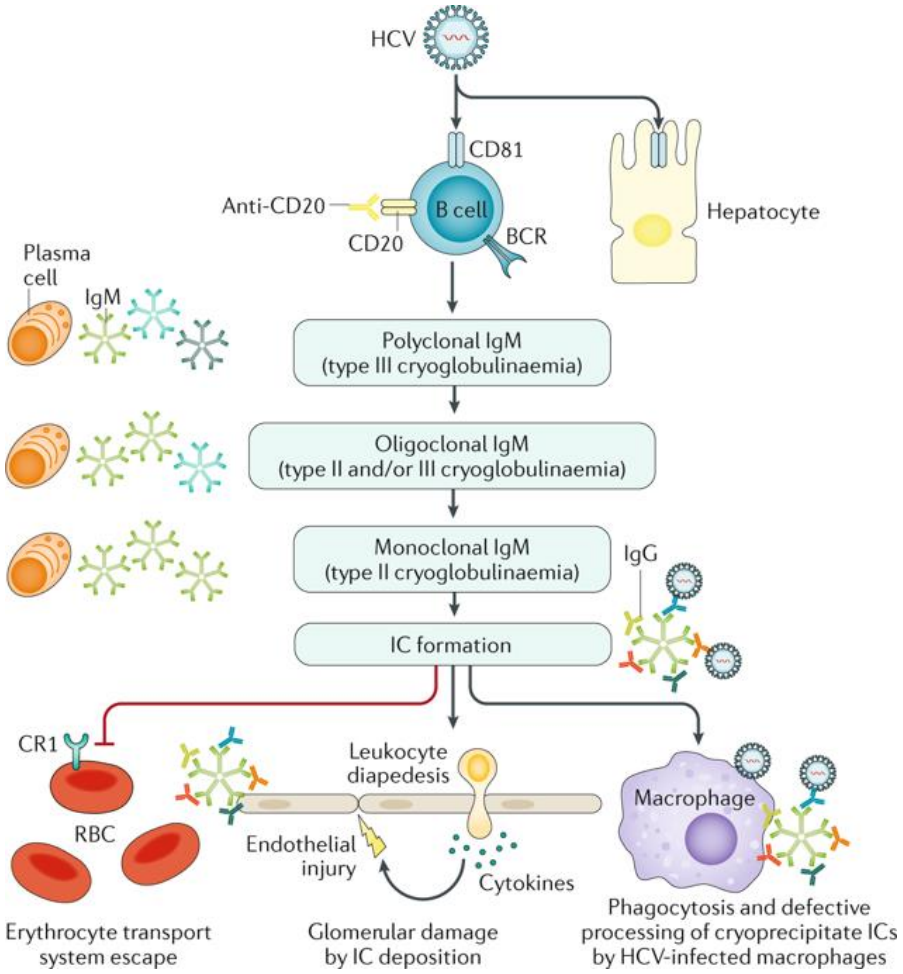
C3 +++; IgM ++; C4 + and C1q + intramembranous /subendothelial



11/18 sclerotic glomeruli.



Is there a point of no return?



- ***Virus eradication does not imply that the immunological process has been stopped***
- ***Several patients continue to have B lymphocyte clonal expansion after SVR***
- ***Persistence of B-cell clone after the cure of HCV infection also promotes disease relapse***
- ***DAAs therapy in HCV-MC:***
  - ***high virological response***
  - ***immunological, hematological and clinical responses limited***

Roccatello, D. et al. (2018) Cryoglobulinaemia
Nat. Rev. Dis. Primers doi.org/10.1038/s41572-018-0009-

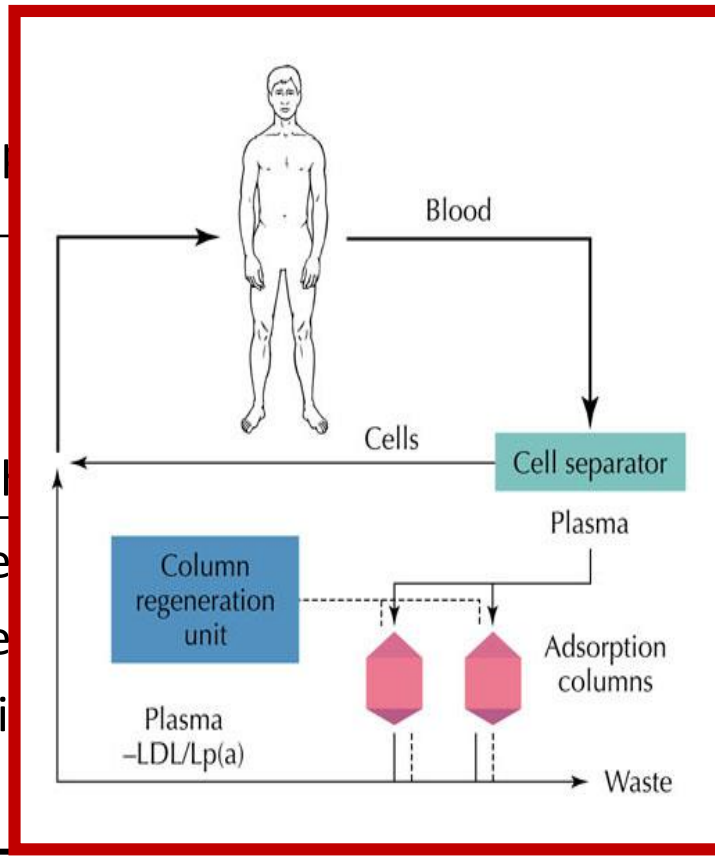
AGENDA

- Cryoglobulinemic glomerulonephritis
- Pathogenesis, presentation and prognosis
- Anti-viral therapy
- **Standard immunosuppression**
- The impact of B cell depletion therapy
- International therapeutic guidelines

DAA schedule

		Duration
	0.5-1 mg /Kg/day	Tap
ESCALAT. 1	**CYC or MMF**	for each
ESCALAT. 2	**Plasma exchange** or **double filtration:** one plasma volume (50 ml/Kg) per session.	3 se 2 se Mai

ulses IV;



CORE CONCEPTS IN PARENCHYMAL KIDNEY DISEASE, Fervenza et al, eds
Therapy of Mixed Cryoglobulinemia Dario Roccatello and Antonello Pani

AGENDA

- Cryoglobulinemic glomerulonephritis
- Pathogenesis, presentation and prognosis
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- **The impact of B cell depletion therapy**
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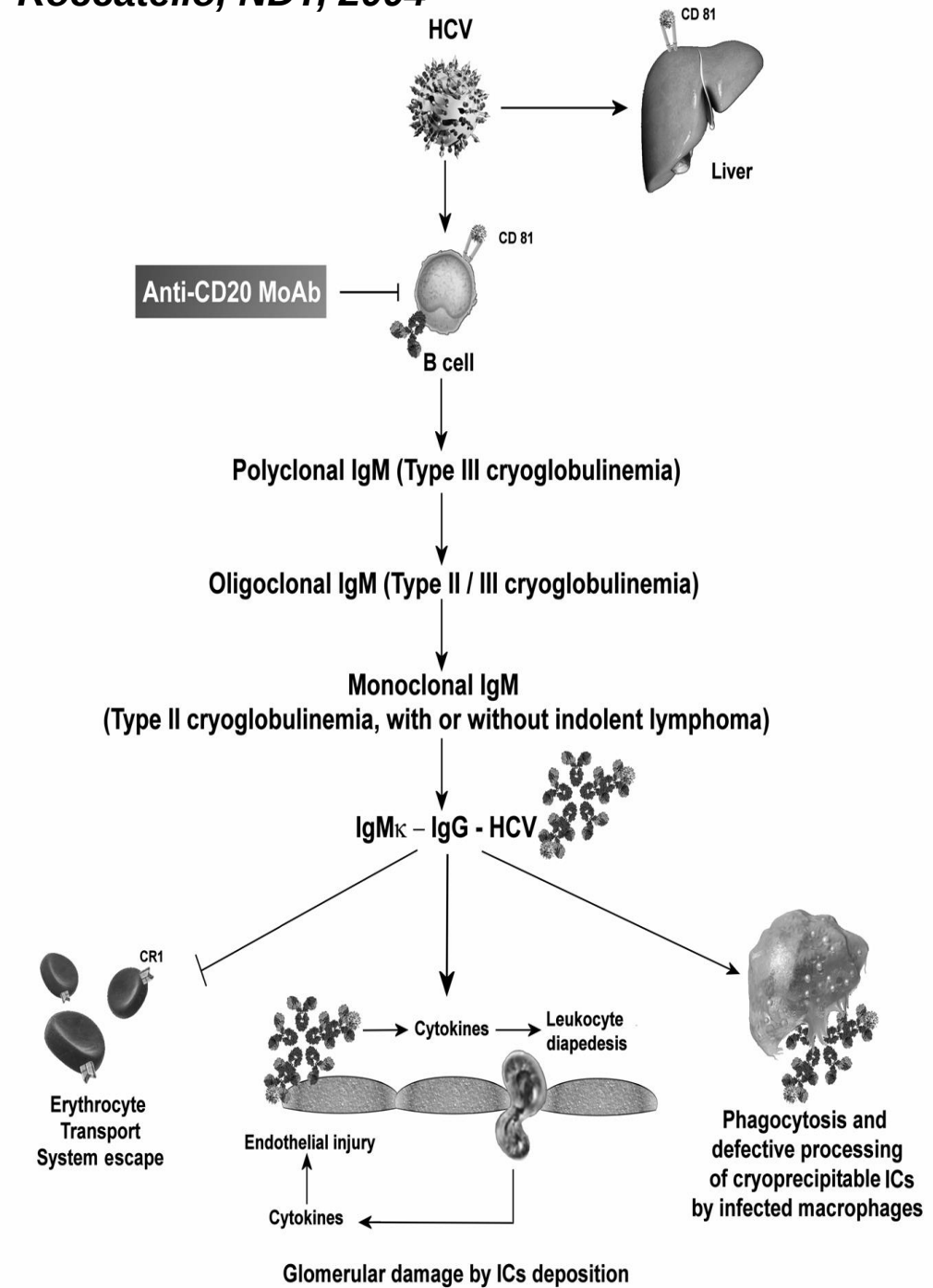
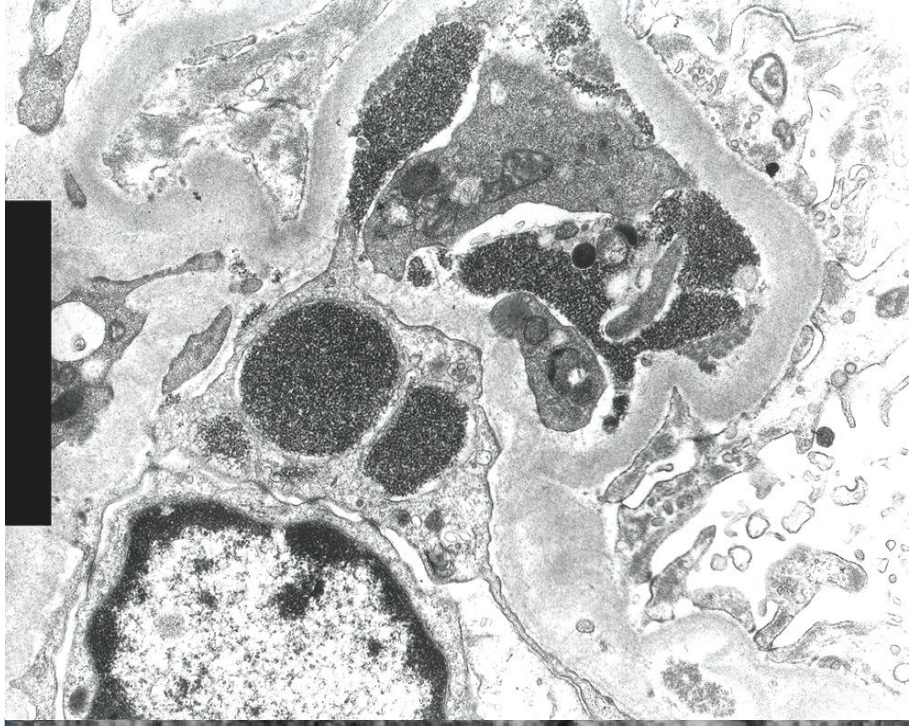
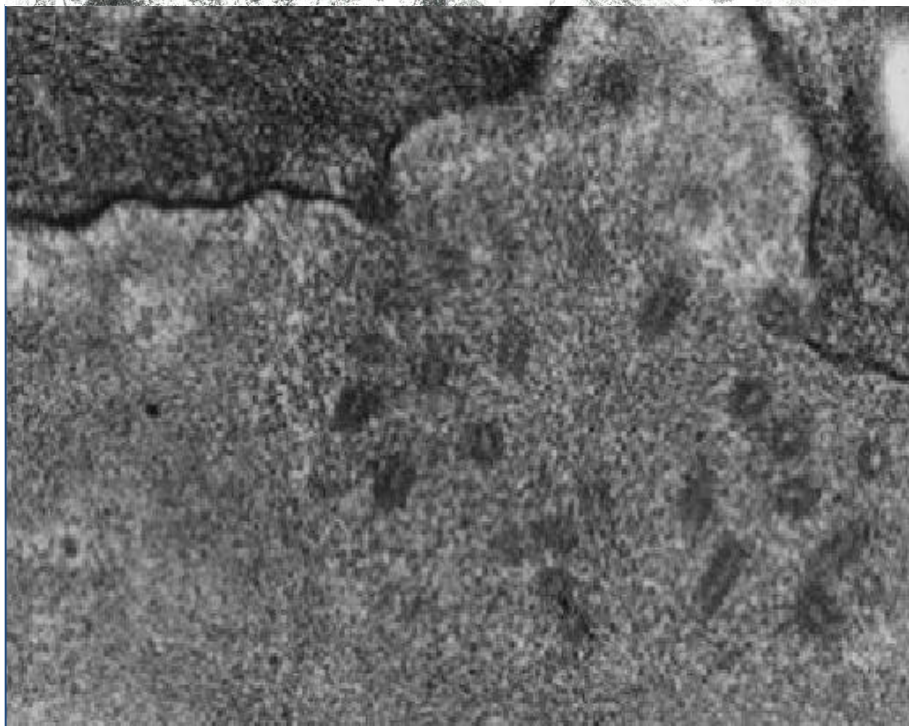
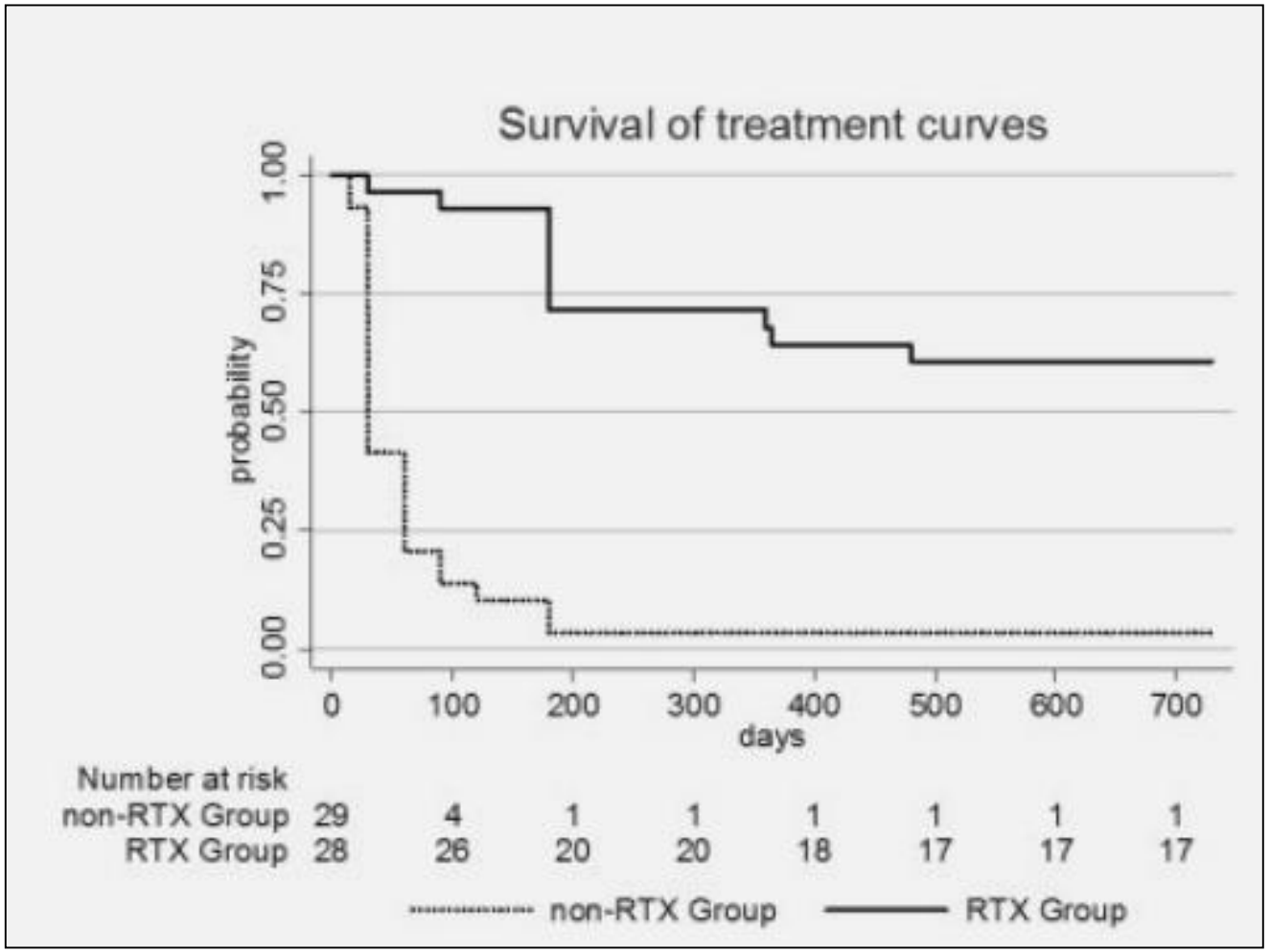
Roccatello, NDT, 2004



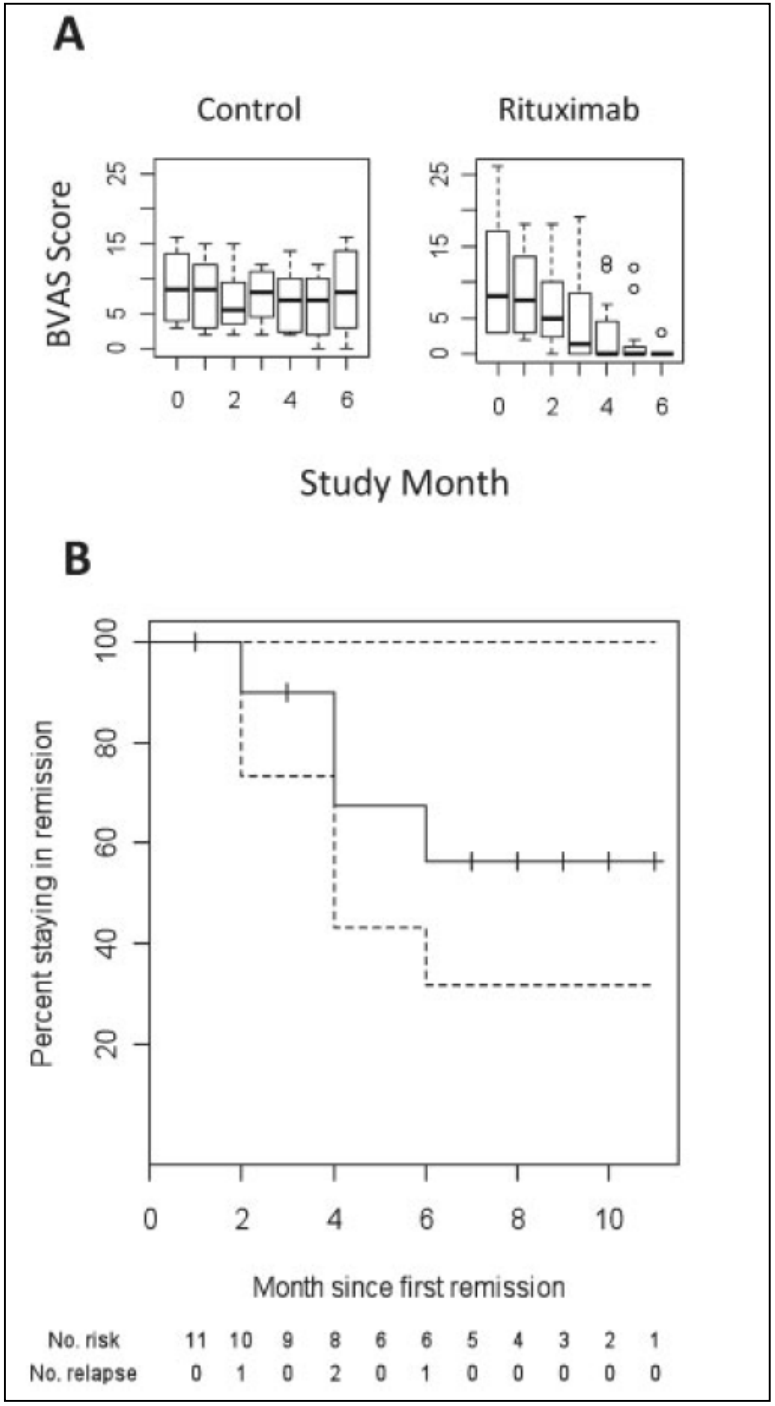




Survival curves in patients randomized to receive rituximab (RTX) therapy or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis.



De Vita S, ARTHRITIS & RHEUMATISM 2012



BVAS and duration of remission **in patients with HCV–associated MC vasculitis randomized to receive RTX or control therapy (maintenance or increased immunosuppressive therapy**

Sneller MC, ARTHRITIS & RHEUMATISM 2012

MC patients treated with Rituximab with a mean follow-up of 72,5 months

31 pts, *29 HCV-infected,* **mean age years 59.8 years; range,** 35-78 years

intolerance to standard therapy	12
resistance to standard therapy	9
severe BM lymphocyte infiltration	5
front-line therapy	5

16 with severe renal involvement (diffuse MPGN or renal vasculitis)

29 peripheral neuropathy

9 large skin ulcers (necrotizing in 7)

Rituximab: 4 plus 2 protocol (Roccatello, NDT 2004): ***375 mg/m^2 on days 1, 8, 15 and 22 with two more doses*** *administered 1 and 2 months later.*

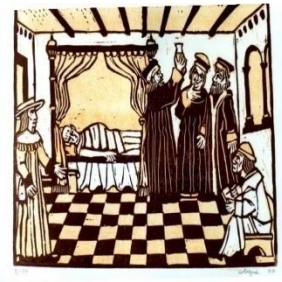
Follow-up: 15-36 months 8 pts

36-60 months 6 pts

60-100 months 10 pts

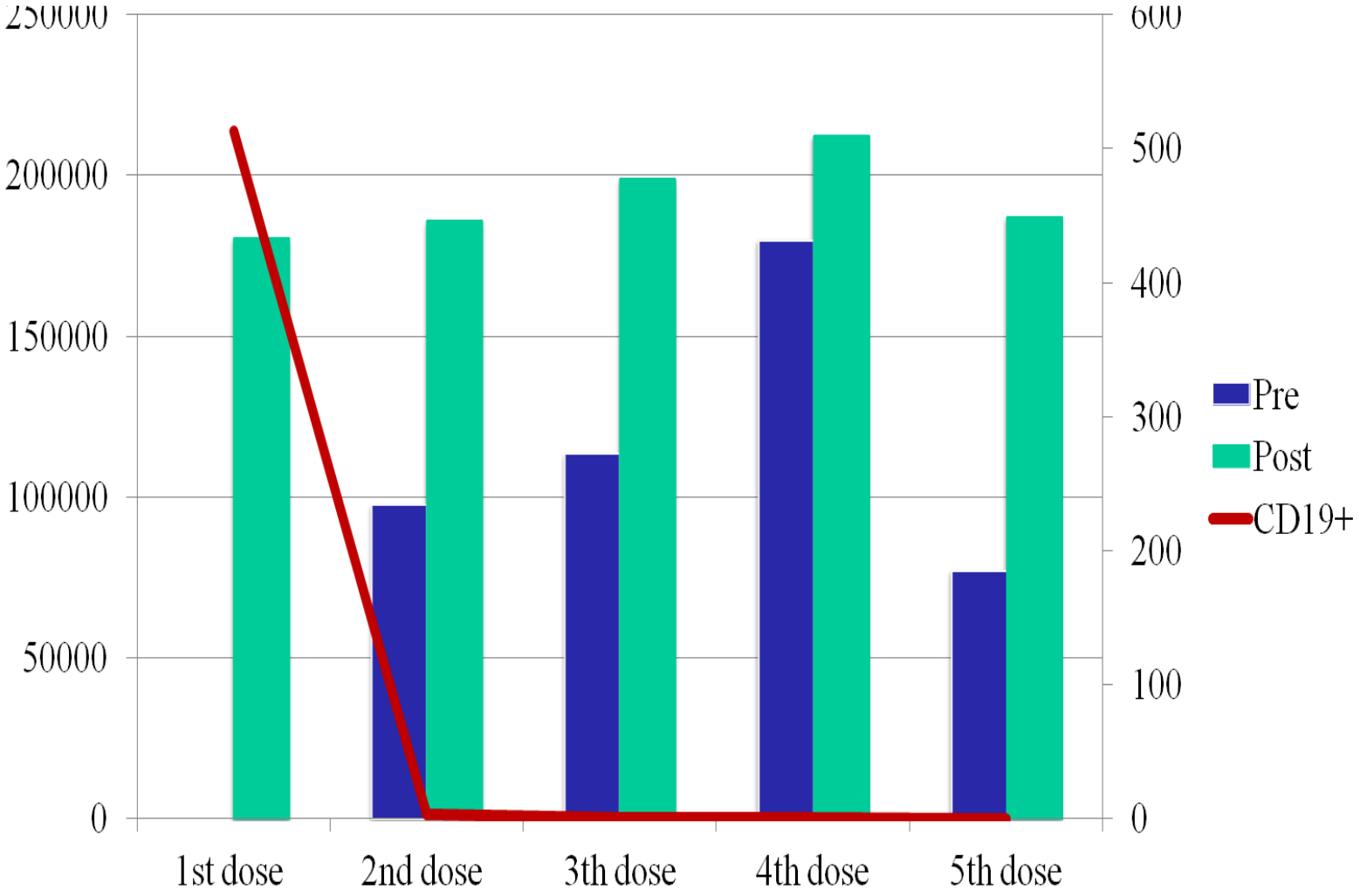
>100 months 6 pts

1 pt lost from the follow-up after 60 months



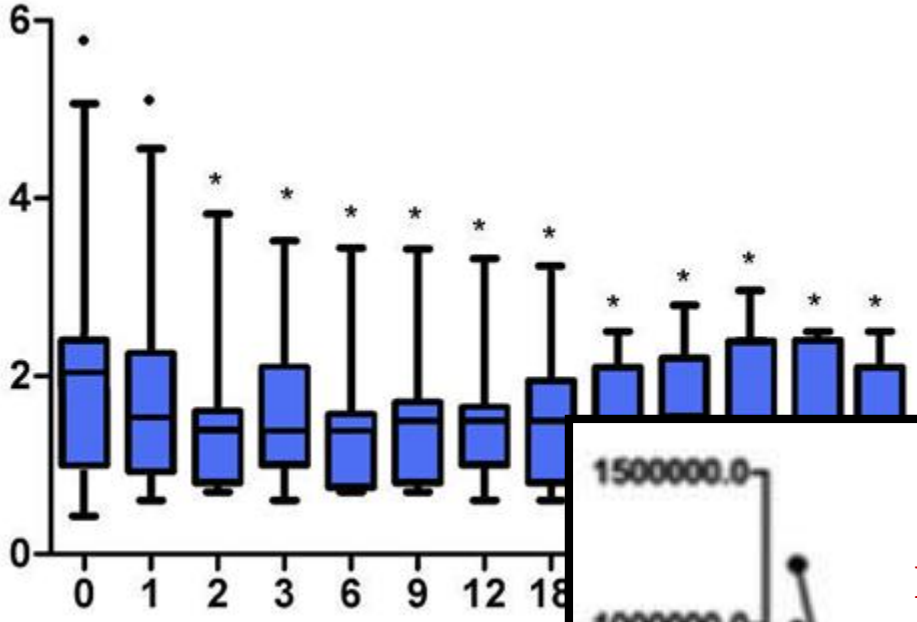
Roccatello et al. ***Current Opinion in Rheumatology 2019***

RTX dosage and CD19+ count

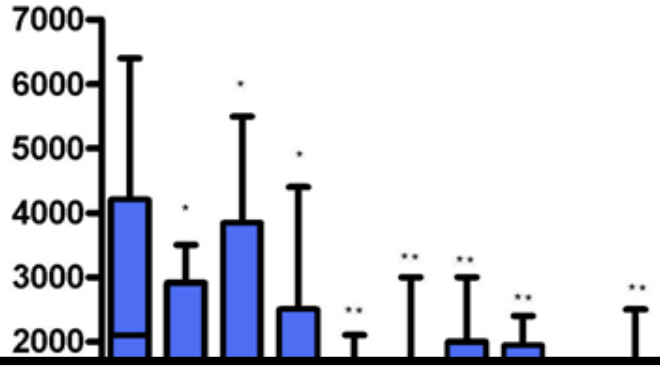


Laboratory profiles of 16 patients with cryoglobulinemic nephritis undergoing a 4 plus 2 infusion protocol of RTX

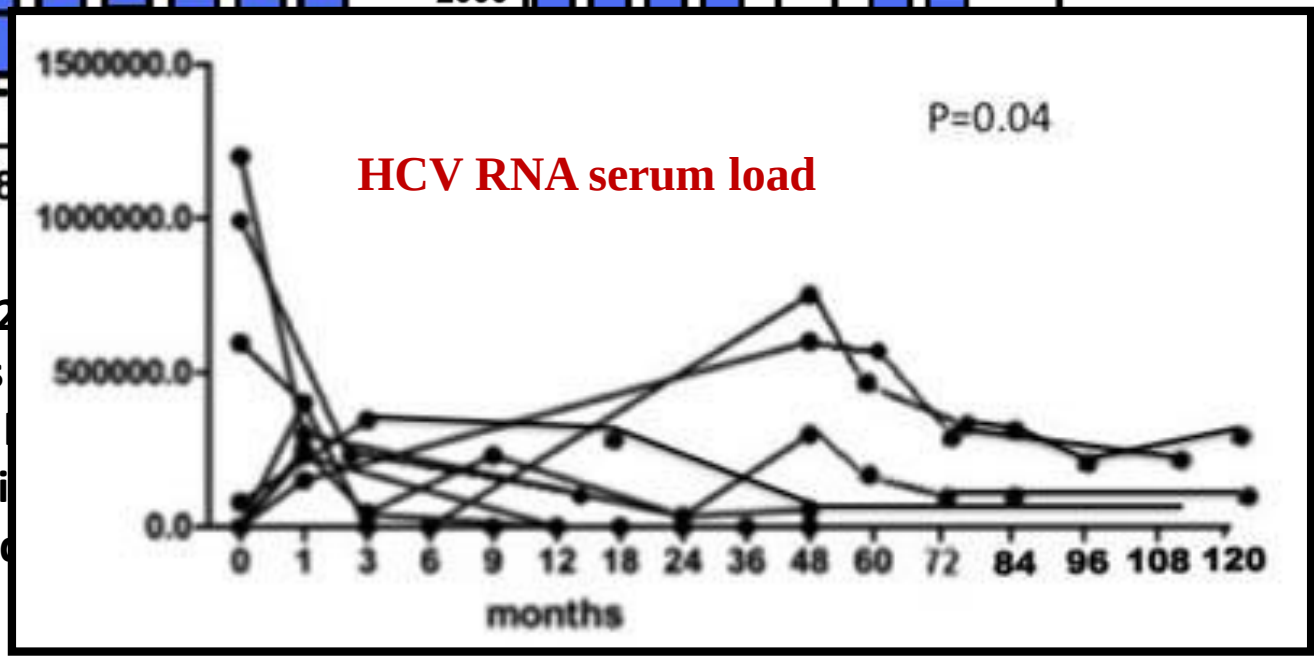
Serum creatinine **(mg/dl)**



Proteinuria **(mg/24 hrs)**



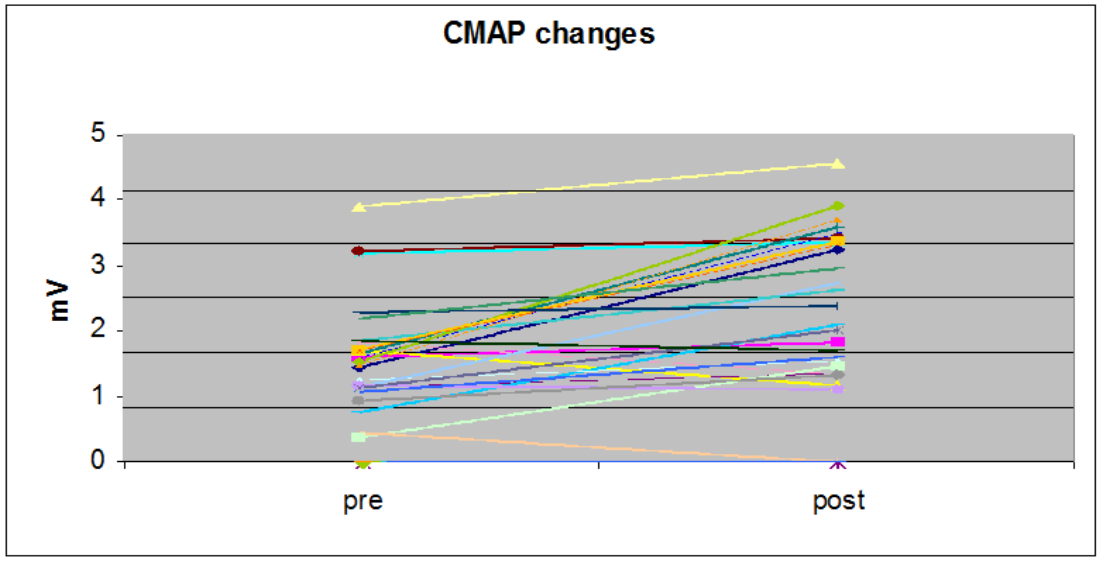
- **Mean follow-up 54.3 (12**
- **Re-inductions in 9 cases**
- **Dose prednisone at the**
  10 pts *without* mai
  3 pts *with 2.5* mg/



Cryoglobulinemic polyneuropathy in 26 pts: EMG changes after anti-CD 20 MoAb

Roccatello et al. *Current Opinion in Rheumatology 2019*

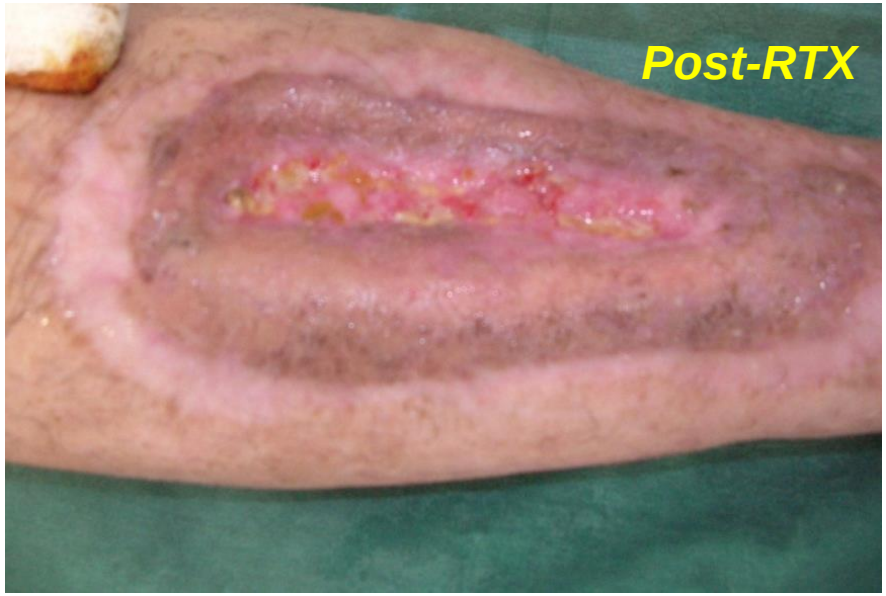
		PRE	POST	*p*
SPE ampl	mV	1.11±1.25	1.53±1.49	0.047
SPE MCV	m/s	43.79±8.9	42.99±8.45	n.s.
SPE Lat	ms	4.07±1.65	4.28±1.56	n.s.
Sural ampl	μV	0.77	6.79	0.079
Sural SCV	m/s	36.87±1.12	49.32±6.02	0.02



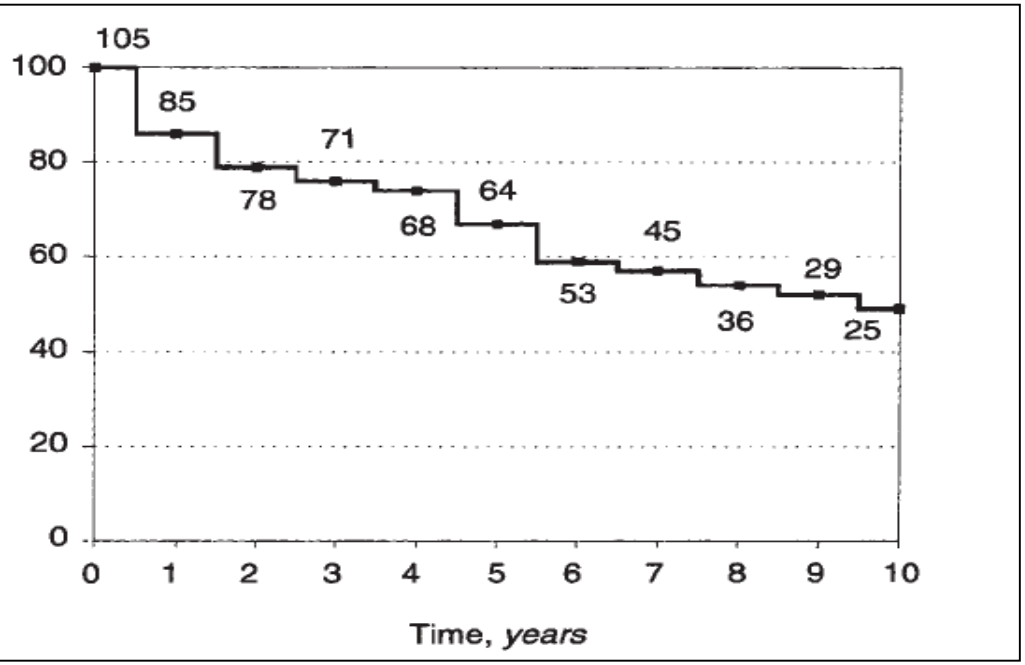
1.1±1.2 ***p< 0.047*** **1.5±1.4**

Paresthesia *26* pts to 4
Burning feet in 7 to 2.
Muscle asthenia in 19 to 3

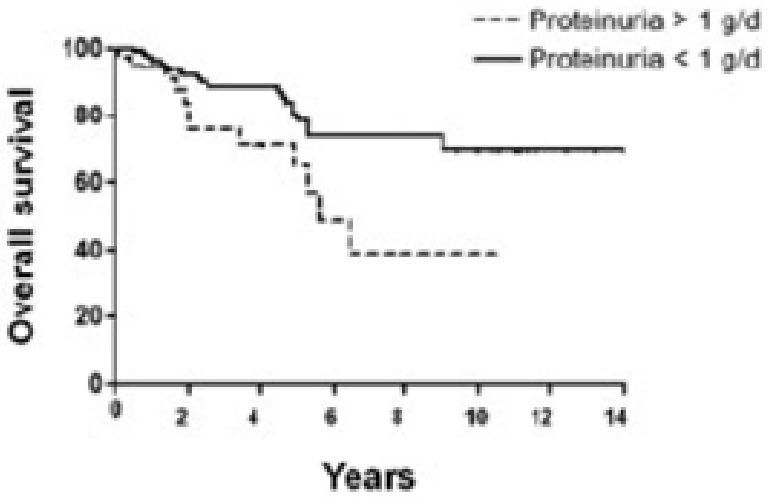
“4 plus 2” Rituximab protocol: effects of therapy



Tarantino, Kidney Int 1995

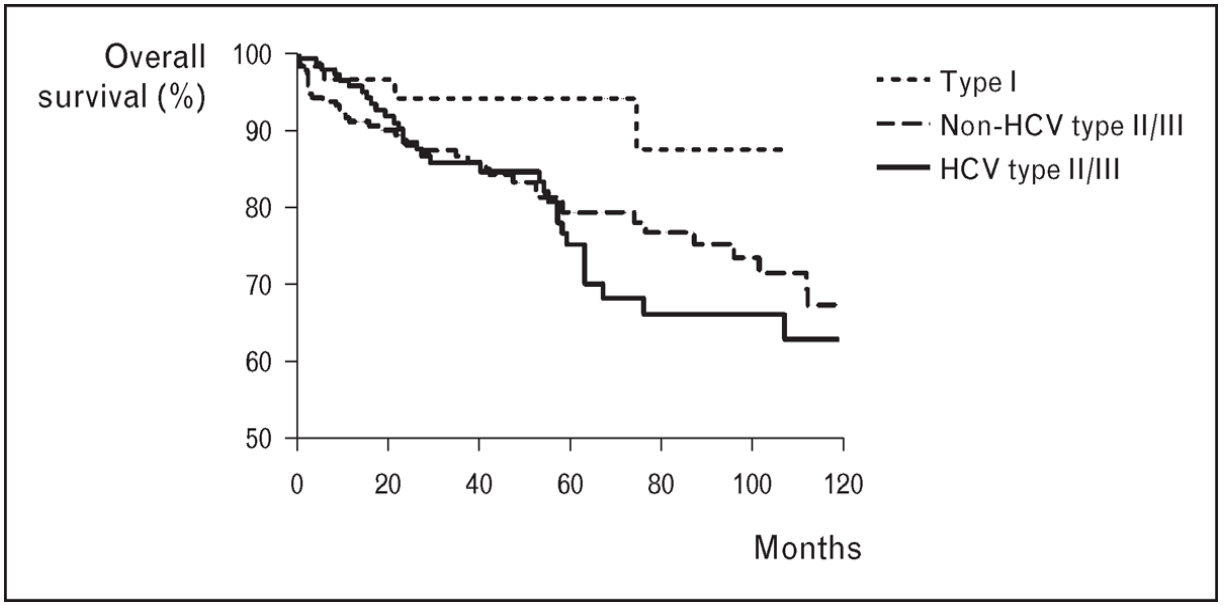


Terrier B, Arth & Rheum 2011

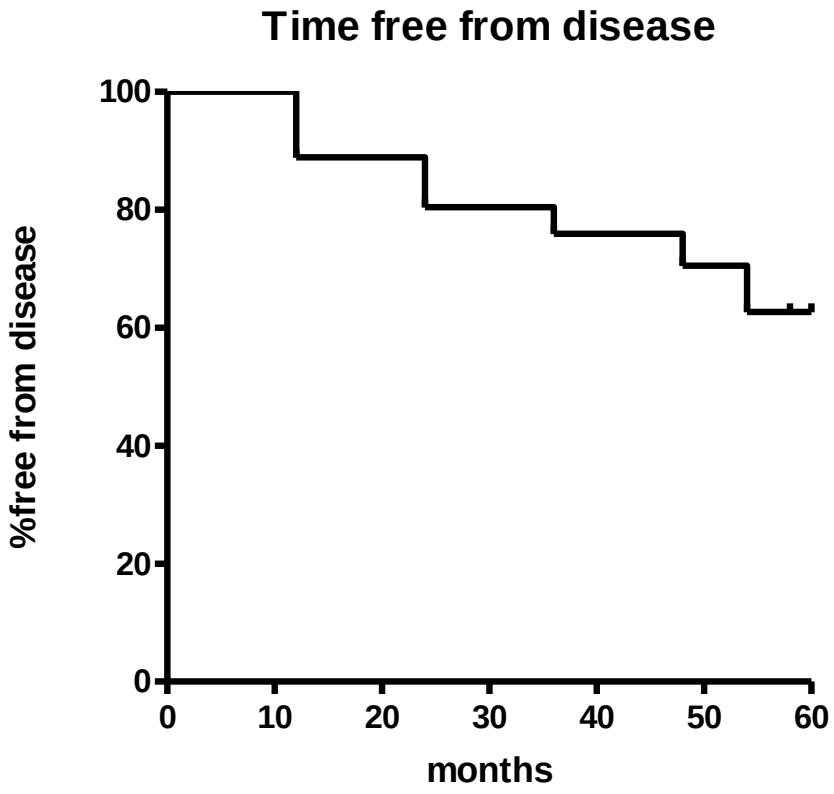


Cumulative probability of survival

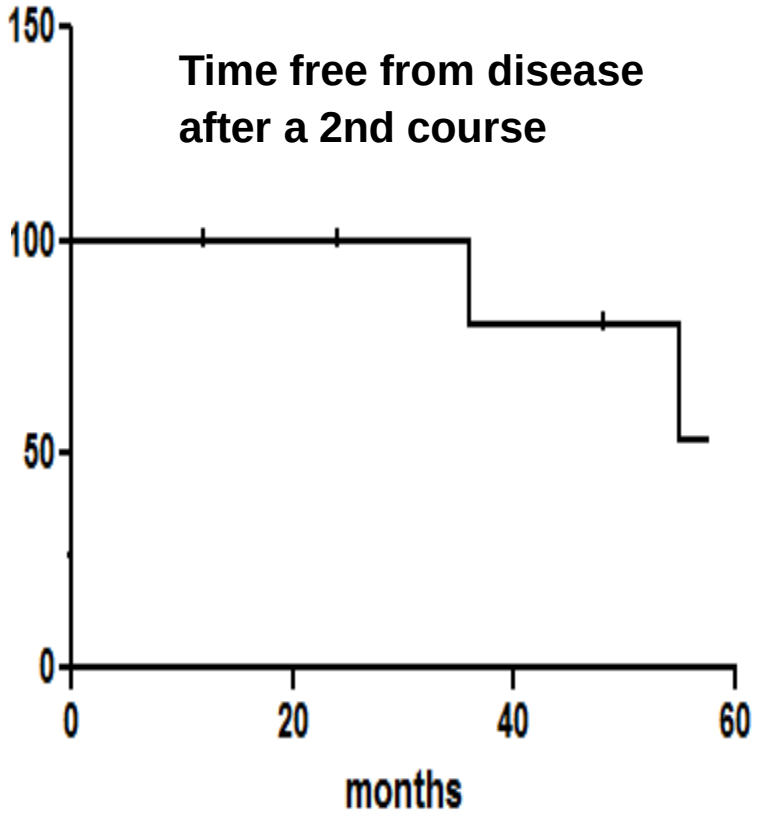
Terrier B, Cur Opin Rheumatol 2013



"4 plus 2" Rituximab protocol: duration of effects



After 6 years the survival rate was 75% and the probability of remaining symptom-free for 10 years without any therapy was 60% after a single "4 plus 2" infusion cycle,

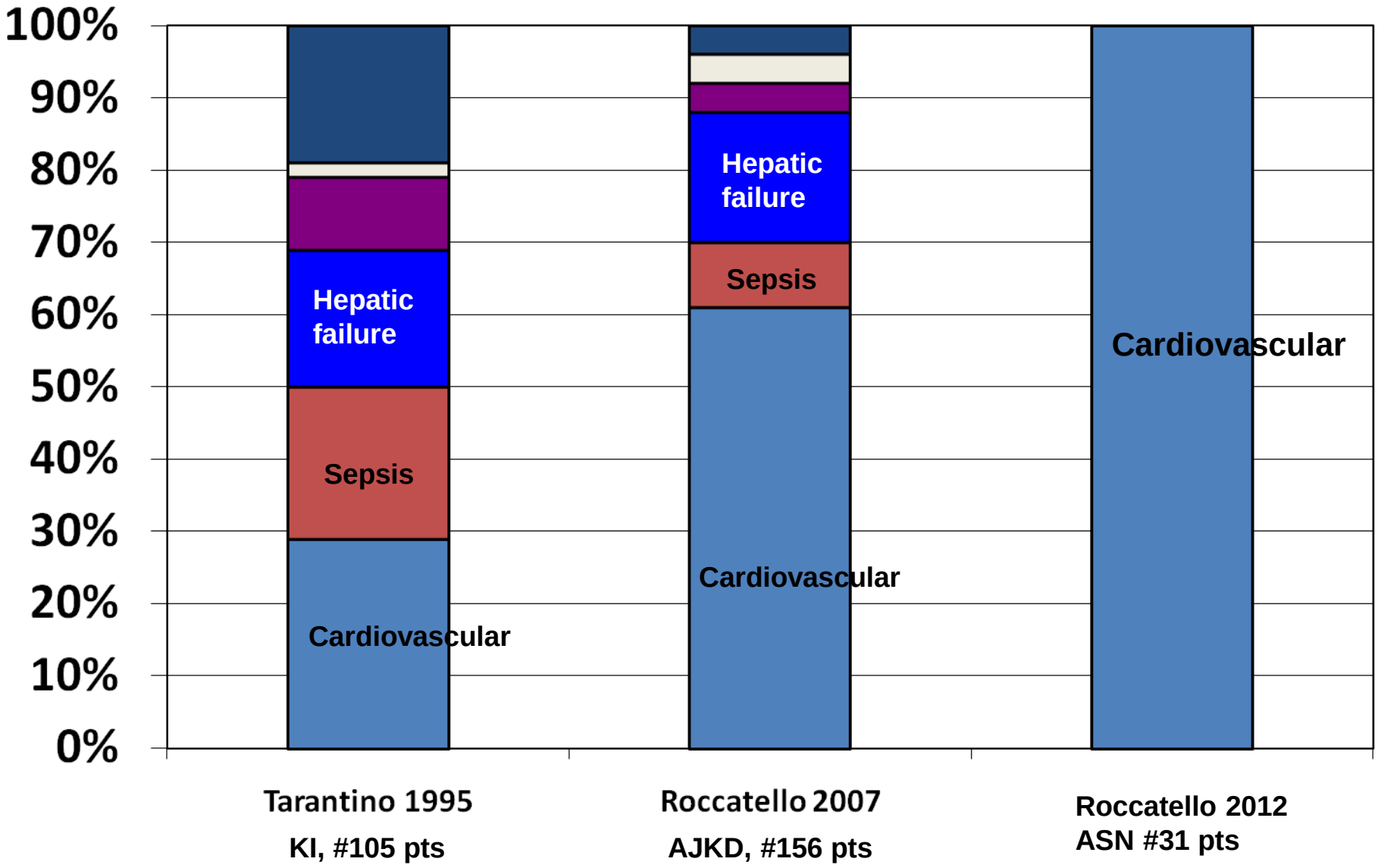


Reinduction

9 pts after 31.1 months with likelihood of living symptom-free for 5 years after relapse was 80%

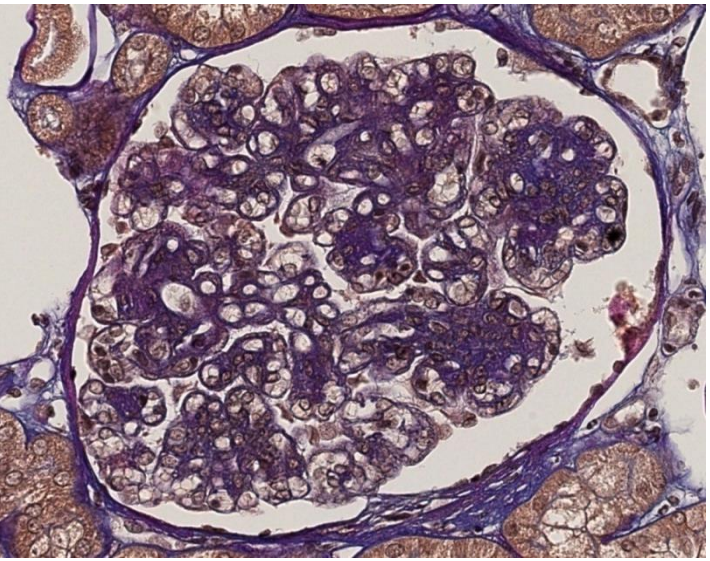
Roccatello *Current Opinion in Rheumatol* 2019

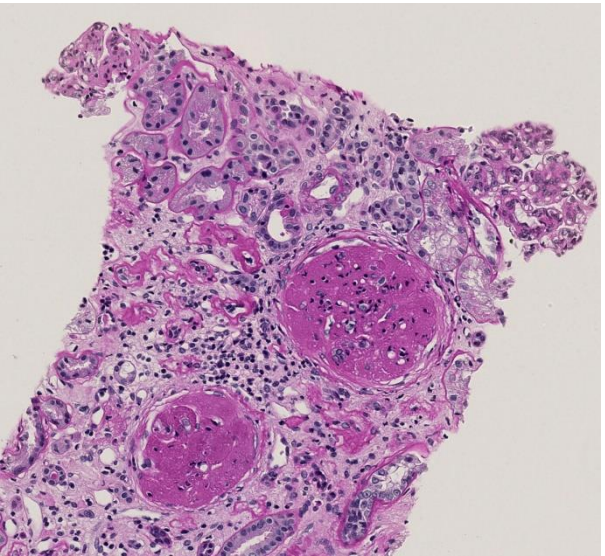
Causes of death in MC patients



The case #1 of the 55-year-old man with chronic hepatitic C and cryoglobulinemc nephritis

Post DAA biopsy



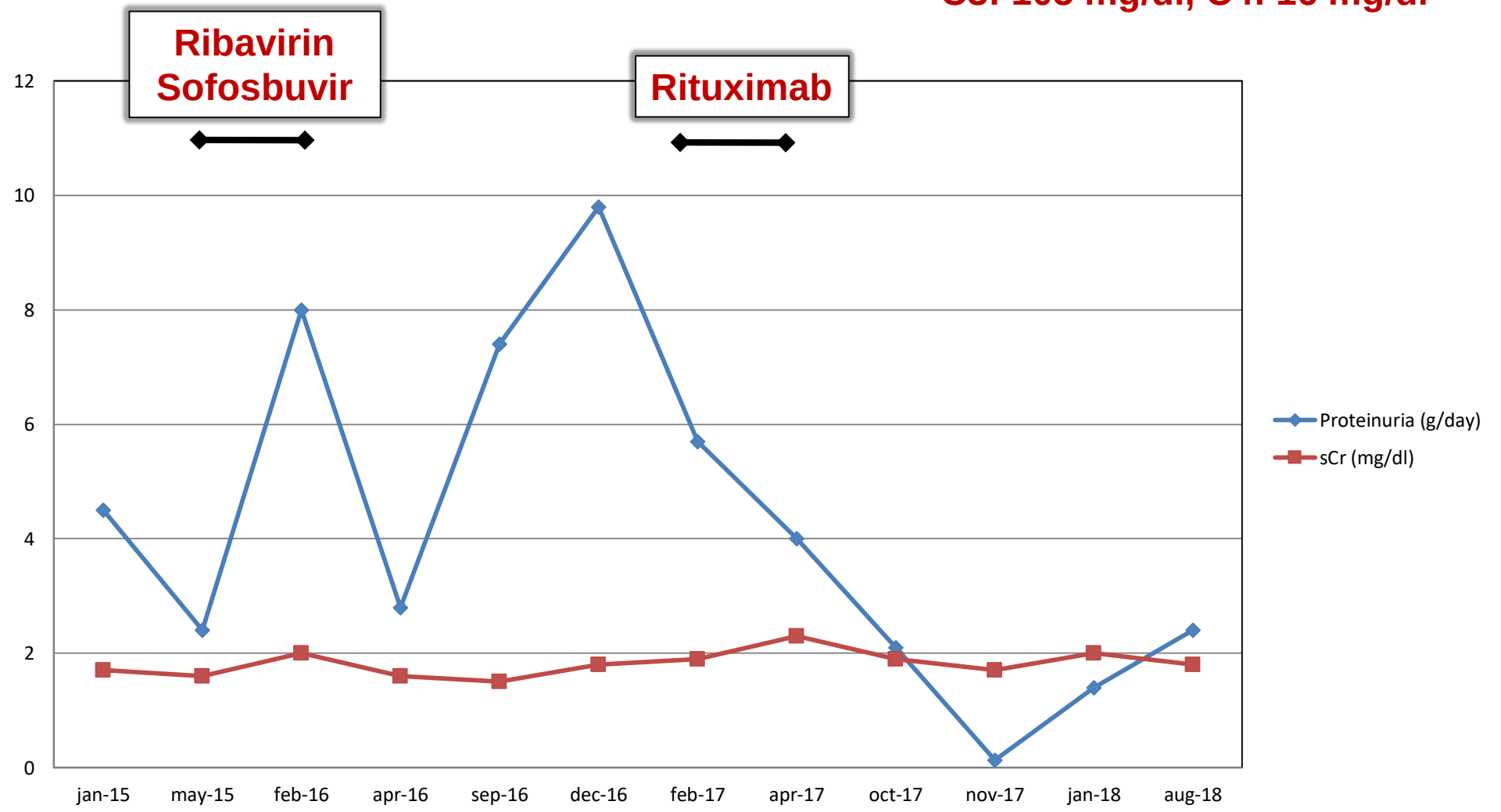


Post DAA lab data

HCV RNA *neg*
sCr *1.9 mg/dl*
Proteinuria *5.7 g/day*
Microscopic haematuria

Treatment with *Rituximab 375 mg/mq* every one week for four doses plus two more doses 375 mg/m2 after 1 and 2 months

HCV RNA negative
sCr 2 mg/dl
Proteinuria 1.4 g/day
Microscopic haematuria neg
C3: 105 mg/dl, C4: 16 mg/dl



AGENDA

- Cryoglobulinemic glomerulonephritis
- Pathogenesis, presentation and prognosis
- Anti-viral therapy
- Standard immunosuppression
- The impact of B cell depletion therapy
- **International therapeutic guidelines**

Table 2 | KDIGO clinical practice guideline on the treatment of HCV-associated glomerulonephritis

Renal presentation	Treatment
Stable kidney function and/or nonnephrotic proteinuria	Direct-acting antiviral therapy
Cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure	Direct-acting antiviral therapy with immunosuppressive treatment, with or without plasma exchange
Histologically active HCV-associated glomerulonephritis that does not respond to direct-acting antiviral therapy	Rituximab as first-line immunosuppressive treatment

UpToDate.

Treatment of the MC syndrome, 2019

Fernando Fervenza, Michael D Leise Dario Roccatello. Robert A Kyle

DAAs plus RTX: which sequence?

At the same time

Advs: **lowering autoimmune response while lowering viral load (and no significant differences in virologic responses compared to the administration of DAA alone)**

Cons: **potential hematologic toxicity**

Sequential DAA before

Mild/moderate arthralgia and purpura might benefit of anti-viral therapy alone

Sequential RTX before (mandatory in MPGN)

RTX could further increase the odds of achieving SVR by depleting B cells which are a potential reservoir for the virus

Consider the entity of viral load and clinical manifestations

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Valerio Veglio (Infectious Diseases)

European Reference Network
for rare or low prevalence complex diseases

Network Kidney Diseases (ERKNet)

NEXT WEBINAR

Enrico Vidal

“Non-infectious complications of peritoneal dialysis in children”.

OCTOBER 29, 4 PM