SPECTRUM OF GLOMERULAR AND VASCULAR KIDNEY PATHOLOGY ASSOCIATED WITH MYELOPROLIFERATIVE NEOPLASMS

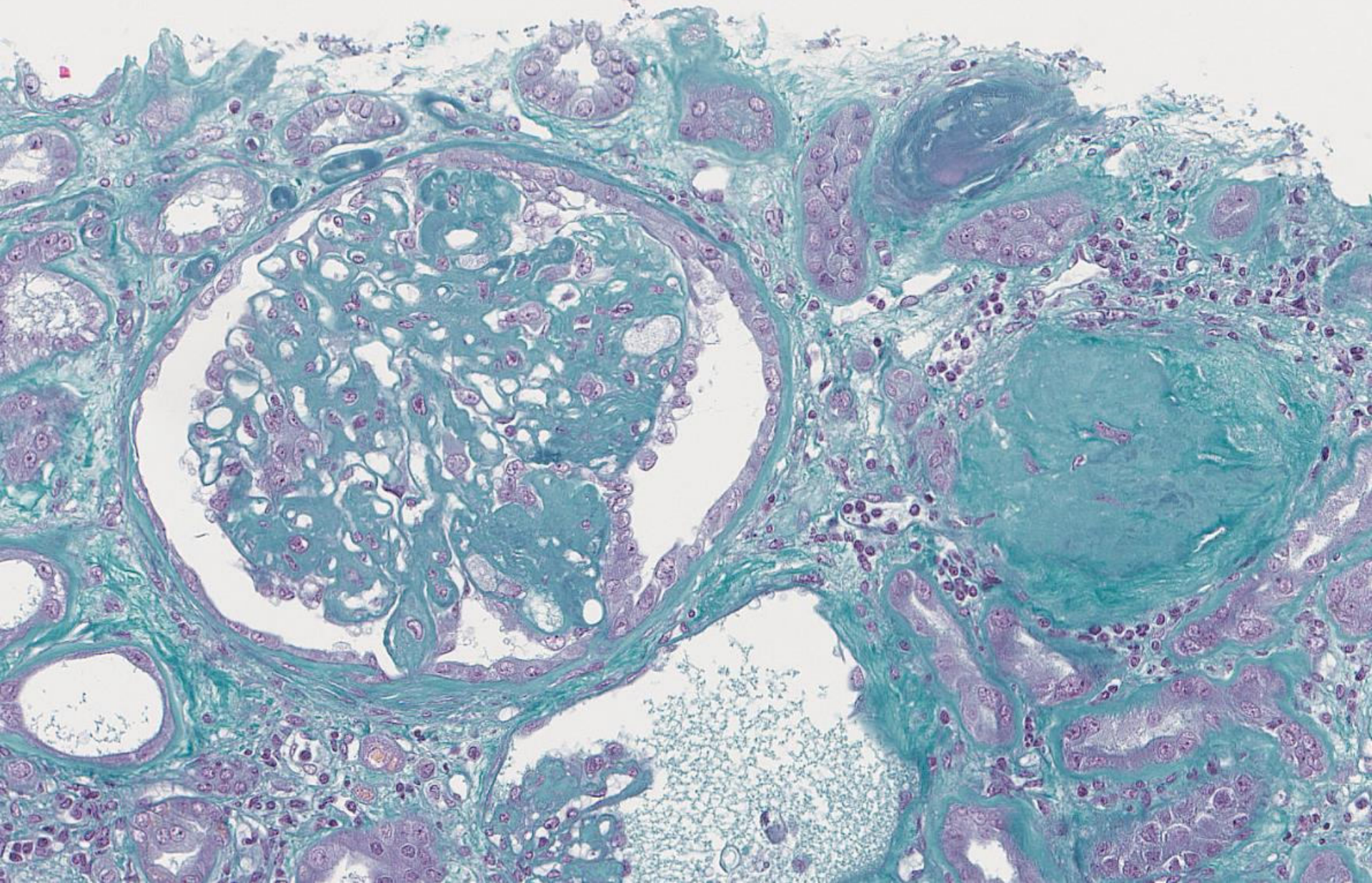
Thibaut d'Izarny-Gargas – 16 mai 2023

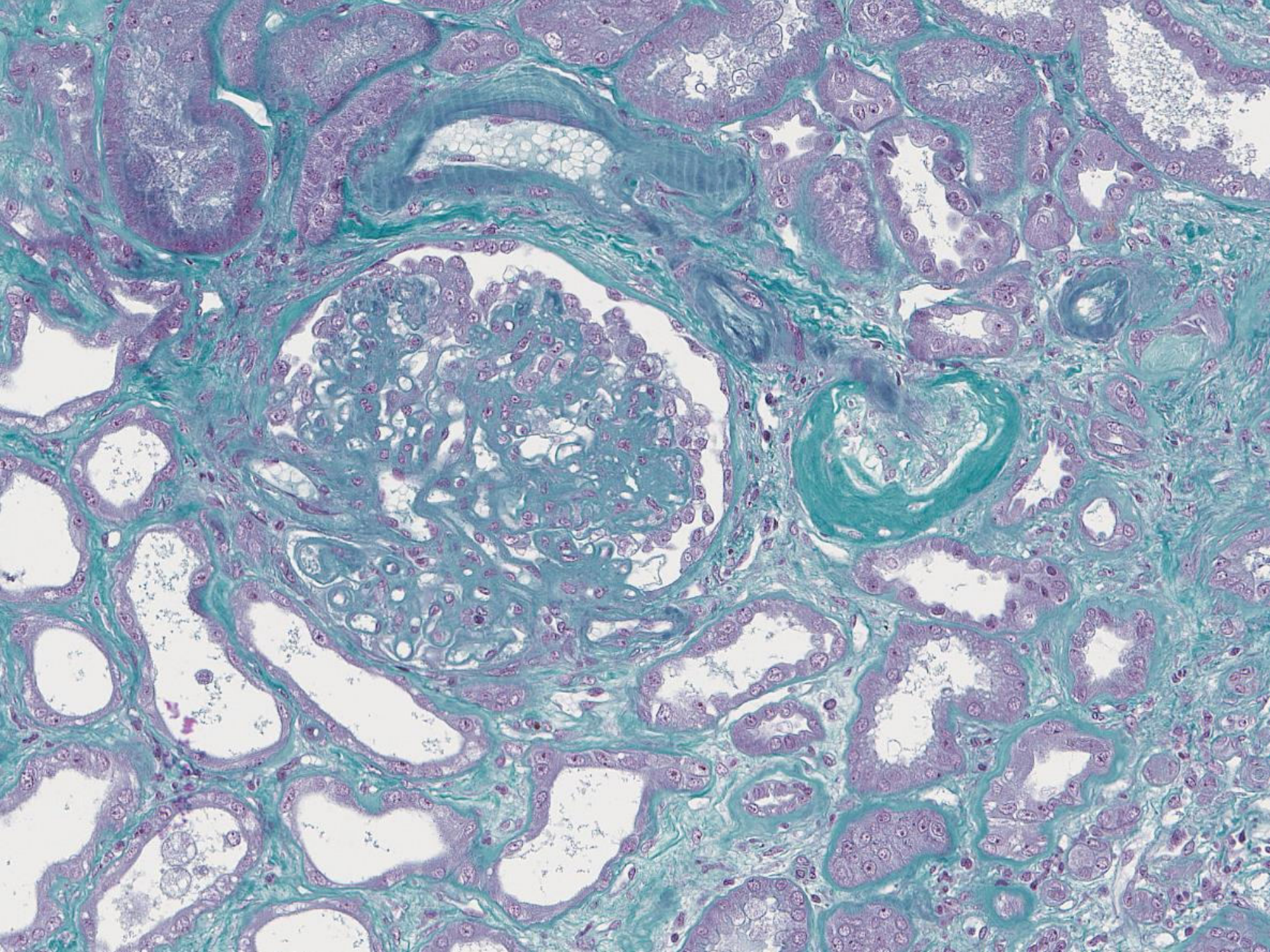
Actualités Néphrologiques Jean Hamburger

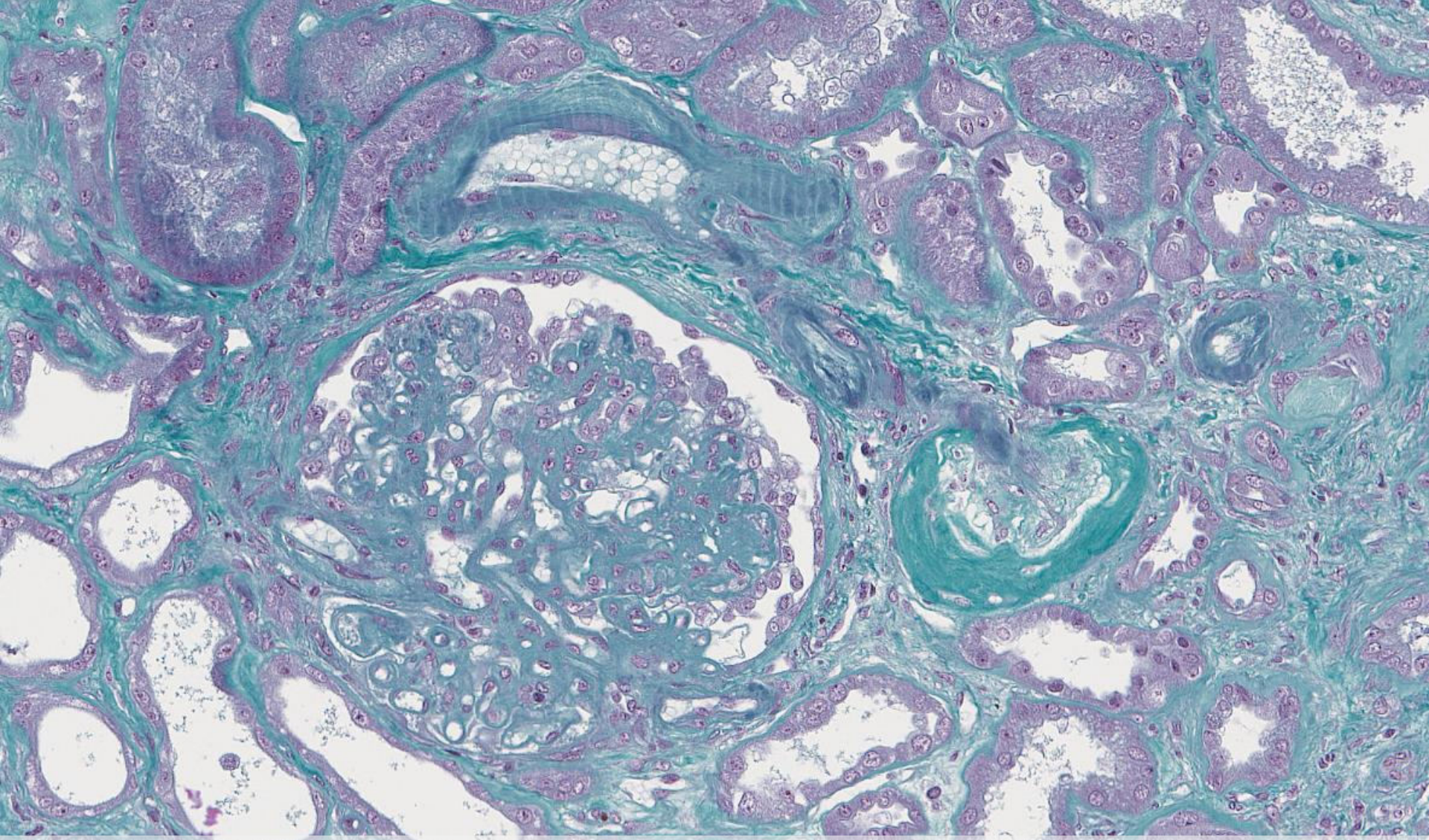
Université Paris Cité

AP-HP. Centre Université Paris Cité

63 year-old woman with **CML**
presenting with **nephrotic syndrome**

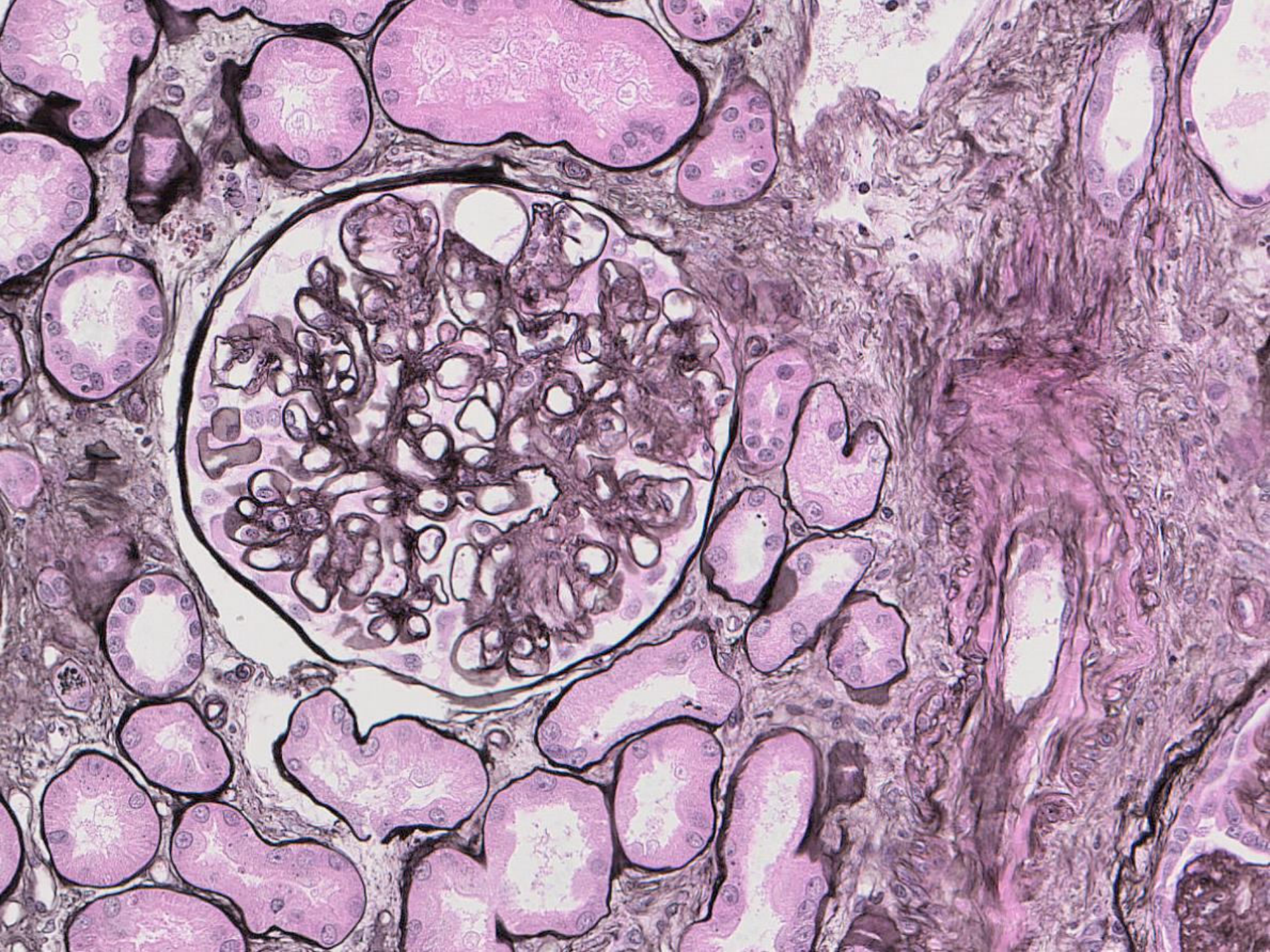


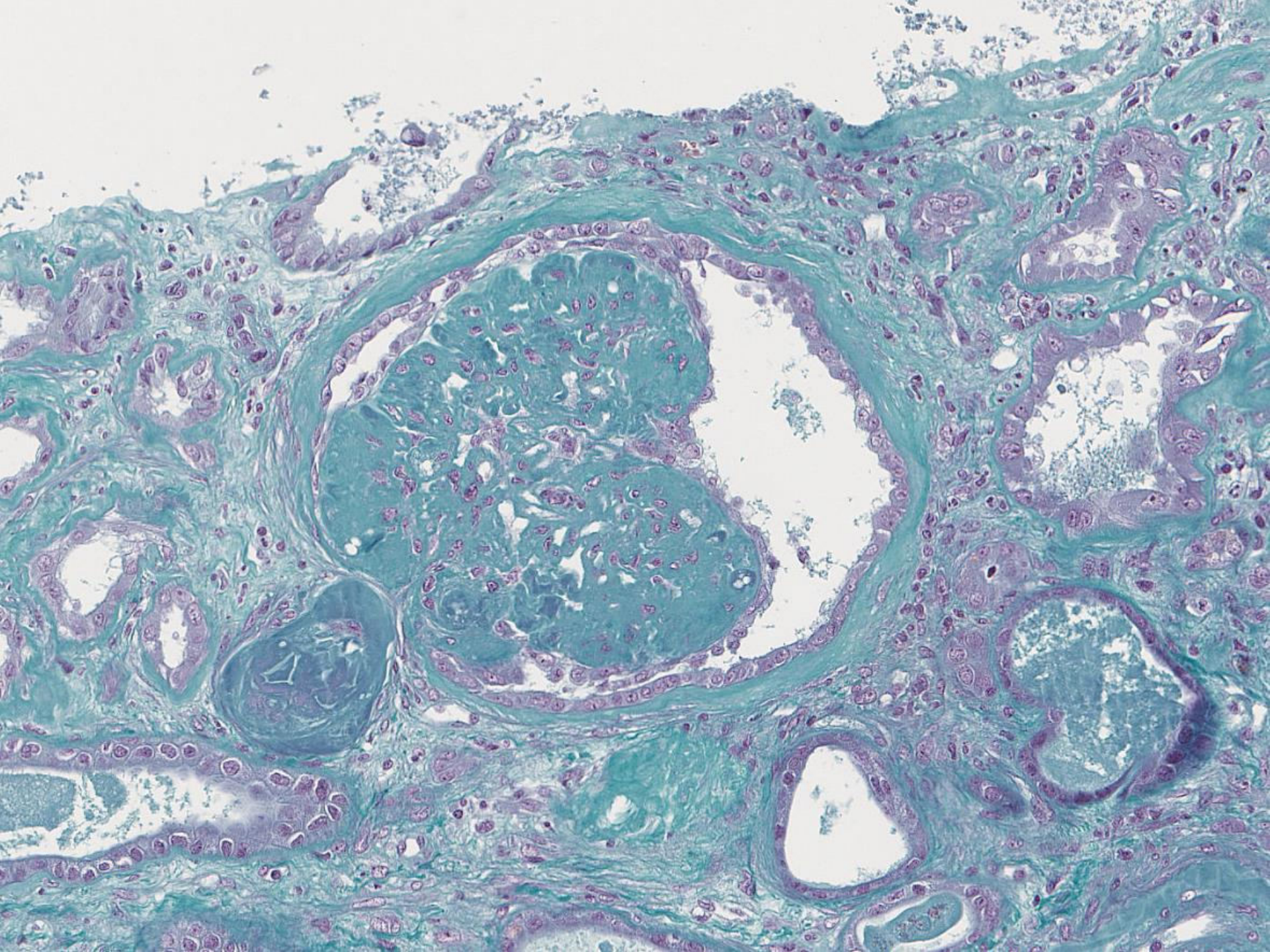




Diabetic kidney disease ?

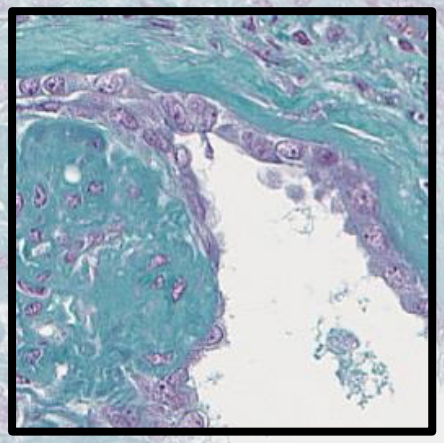
… no diabetes

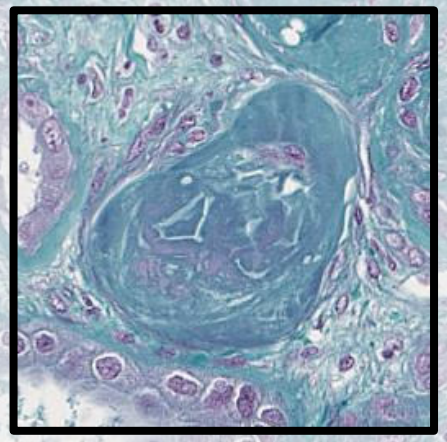




MPN-associated …

Glomerular disease ?





Vascular disease ?

Myeloproliferative neoplasms

2016 WHO classification of MPNs

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*

Arber et al. **Blood** 2016 ; Moliterno & Kaizer **Blood** 2020 ; Hasselbalch et al. **Blood** 2021

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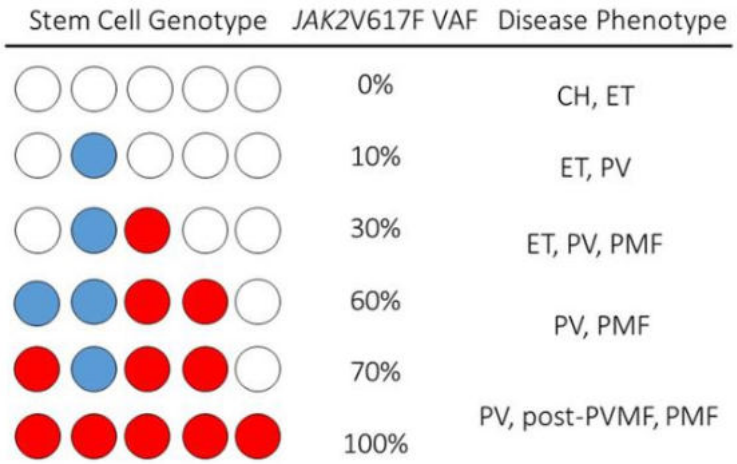

Hematological disease

Acute leukemia conversion
Myelofibrosis progression

Vascular disease

Thrombosis
Hemorrhage
Microvascular disease

Arber et al. **Blood** 2016 ; Moliterno & Kaizer **Blood** 2020 ; Hasselbalch et al. **Blood** 2021

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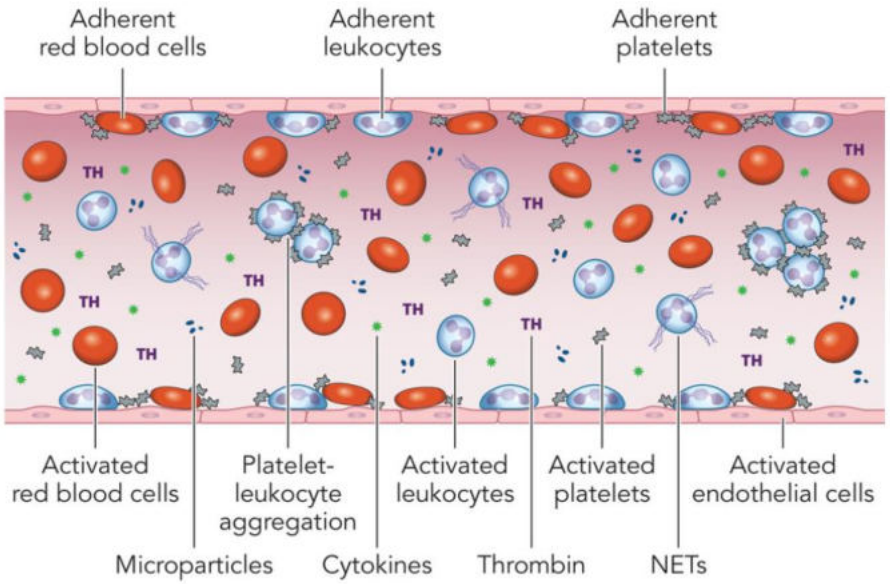

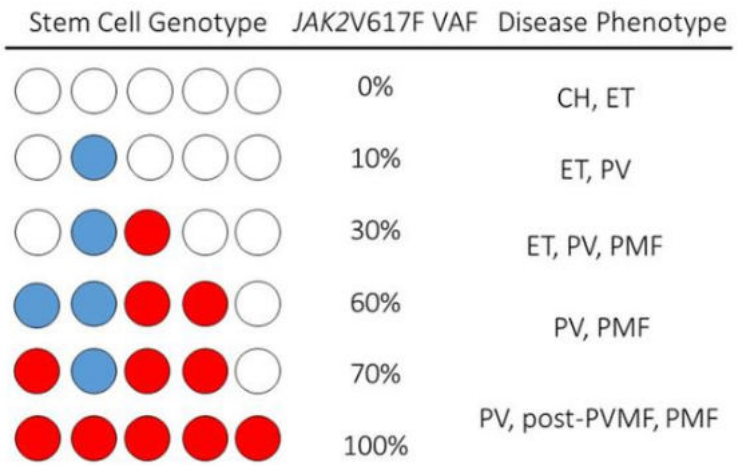

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Acute leukemia conversion
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Chronic kidney disease in MPN patients

eGFR at diagnosis	Unclas. ($n=11$)	Cum. Unclas.	ET ($n=45$)	Cum. ET	PV ($n=58$)	Cum. PV	MF ($n=29$)	Cum. MF	Total ($n=143$)	Cum. Total
15–29*	0.09 (1)	0.09	0.00 (0)	0.00	0.03 (2)	0.03	0.00 (0)	0.00	0.02 (3)	0.02
30–44**	0.18 (2)	0.27	0.07 (3)	0.07	0.03 (2)	0.06	0.10 (3)	0.10	0.07 (10)	0.09
45–59**	0.00 (0)	0.27	0.22 (10)	0.29	0.21 (12)	0.27	0.21 (6)	0.31	0.20 (28)	0.29
60–74	0.09 (1)	0.36	0.27 (12)	0.56	0.35 (20)	0.62	0.28 (8)	0.59	0.29 (41)	0.58
75–89	0.27 (3)	0.63	0.20 (9)	0.76	0.27 (16)	0.89	0.24 (7)	0.83	0.25 (35)	0.83
≥90	0.36 (5)	0.99	0.24 (11)	1.00	0.10 (6)	0.99	0.17 (5)	1.00	0.18 (26)	1.01

Christensen et al. **Leukemia Research** 2016 ; Ren et al. **Ann Hematol** 2019

Chronic kidney disease in MPN patients

eGFR at diagnosis	Unclas. ($n=11$)	Cum. Unclas.	ET ($n=45$)	Cum. ET	PV ($n=58$)	Cum. PV	MF ($n=29$)	Cum. MF	Total ($n=143$)	Cum. Total
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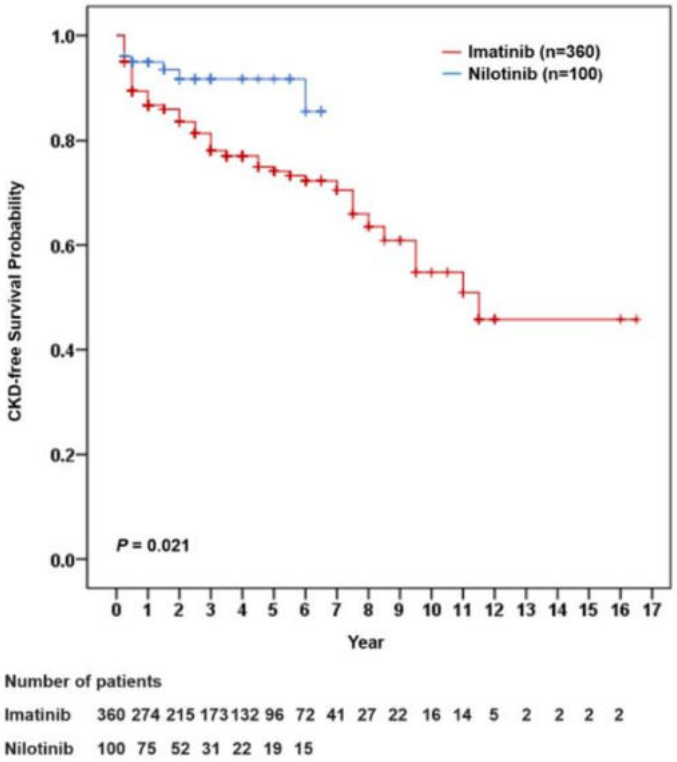
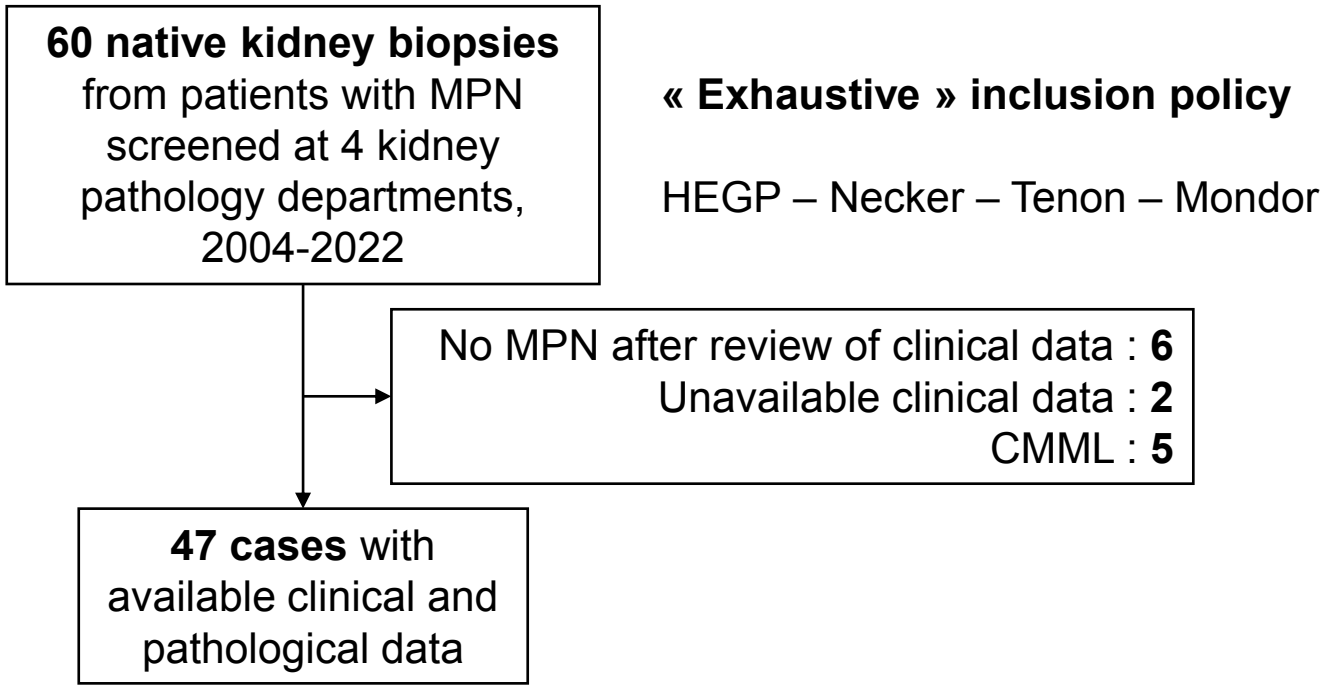


	CKD		
	HR	95% CI	*P*
Interval from diagnosis to starting TKI therapy, month			<0.001
<6 (ref)			
6–11	2.0	0.9–4.1	0.078
12–24	2.6	1.1–6.2	0.031
≥24	4.4	2.4–8.3	<0.001

Christensen et al. **Leukemia Research** 2016 ; Ren et al. **Ann Hematol** 2019

Study design



Study design

60 native kidney biopsies from patients with MPN screened at 4 kidney pathology departments, 2004-2022

« Exhaustive » inclusion policy

HEGP – Necker – Tenon – Mondor

No MPN after review of clinical data : **6**
Unavailable clinical data : **2**
CMML : **5**

47 cases with available clinical and pathological data

- ✓ **Histological review with systematic scoring**
  - Glomerular lesions
  - Vascular lesions
- ✓ **Immunohistochemistry**
  - Glycophorin C
  - Myeloperoxidase
  - Factor VIII
- ✓ **Clinical charts review**
  - Hematological and renal disease
  - Cardiovascular disease and risk factors
  - Renal survival

Clinical features

Sex (%)	
Male	30 (63.8)
Female	17 (36.2)
Age at kidney biopsy, years	60.8 (12.1)
Time since MPN diagnosis, years	8.0 (6.7)
MPN diagnosis (%)	
Chronic myeloid leukemia	16 (34.0)
Polycythemia vera	14 (29.8)
Essential thrombocythemia	10 (21.3)
Primary myelofibrosis	7 (14.9)
Driver mutation (%)	
BCR-ABL fusion	16 (36.4)
JAK2	22 (50.0)
CALR	2 (4.5)
MPL	1 (2.3)
Not identified (*JAK2*-negative)	3 (6.8)
Hematological complications (%)	
Secondary myelofibrosis	4 (8.5)
Acute lymphoblastic leukemia	1 (2.1)
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Diabetes mellitus (%)	14 (29.8)
Hypertension (%)	40 (85.1)
Number of antiHTN drugs	2.4 (1.3)
Dyslipidemia (%)	20 (42.6)
Smoking history (%)	19 (45.2)
Biopsy indication (%)	
Chronic kidney disease	26 (55.3)
Acute kidney injury	9 (19.1)
Nephrotic syndrome	6 (12.8)
Proteinuria / hematuria	6 (12.8)
Creatinine, µmol/L	211.8 (136.8)
eGFR, mL/min/1.73 m²	38.2 (25.9)
uPCR, g/g	3.4 (3.8)

Diagnoses after pathological review

MPN-related glomerulopathy	14 (29.8)
Membranous nephropathy	2 (4.3)
IgA nephropathy	2 (4.3)
Focal segmental glomerulosclerosis	2 (4.3)
Diabetic kidney disease	1 (2.1)
Lupus nephritis	1 (2.1)
Minimal change disease	1 (2.1)
Monoclonal immunoglobulin deposition disease	1 (2.1)
Vascular nephropathy	17 (36.2)
Oxalate nephropathy	2 (4.3)
Chronic tubulointerstitial nephritis	1 (2.1)
Acute tubulointerstitial nephritis	1 (2.1)
Acute tubular necrosis	1 (2.1)
Normal	1 (2.1)

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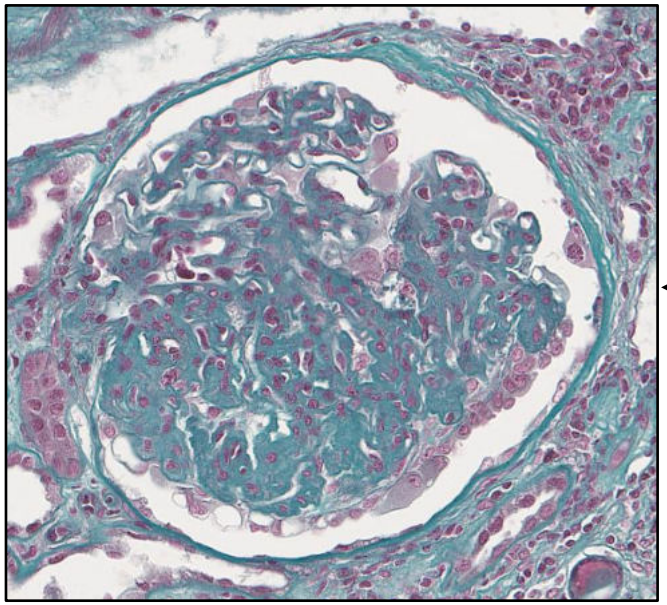
Normal	1 (2.1)

Glomerular disease in myelofibrosis patients

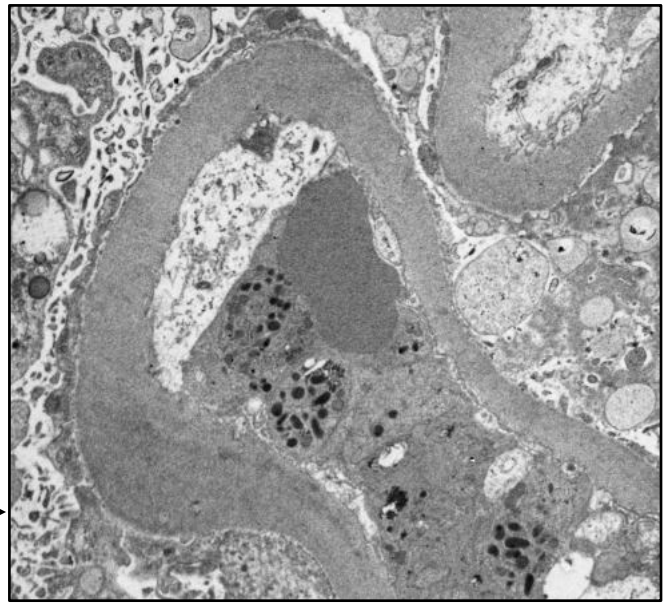
	No myelofibrosis	Myelofibrosis	*P*
n	**36**	**11**	
eGFR, mL/min/1.73 m²	40.3 (27.9)	31.6 (17.7)	0.542
uPCR, g/g	**2.6 (3.3)**	**6.0 (4.3)**	**0.009**
Globally sclerotic glomeruli, %	41.4 (24.2)	40.2 (13.9)	0.867
IF/TA area, %	45.6 (28.3)	41.8 (28.2)	0.736
Mesangial expansion (%)	**11 (33.3)**	**9 (81.8)**	**0.012**
Mesangial hypercellularity (%)	**11 (33.3)**	**8 (72.7)**	**0.035**
Podocytopathy (%)	**13 (37.1)**	**8 (80.0)**	**0.029**
Glomerular TMA (%)	**5 (15.2)**	**4 (40.0)**	**0.177**

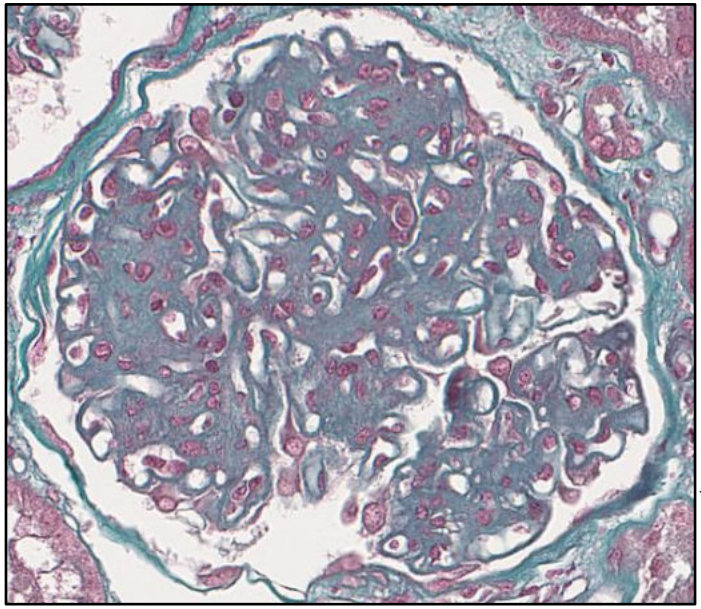
Glomerular disease in myelofibrosis patients



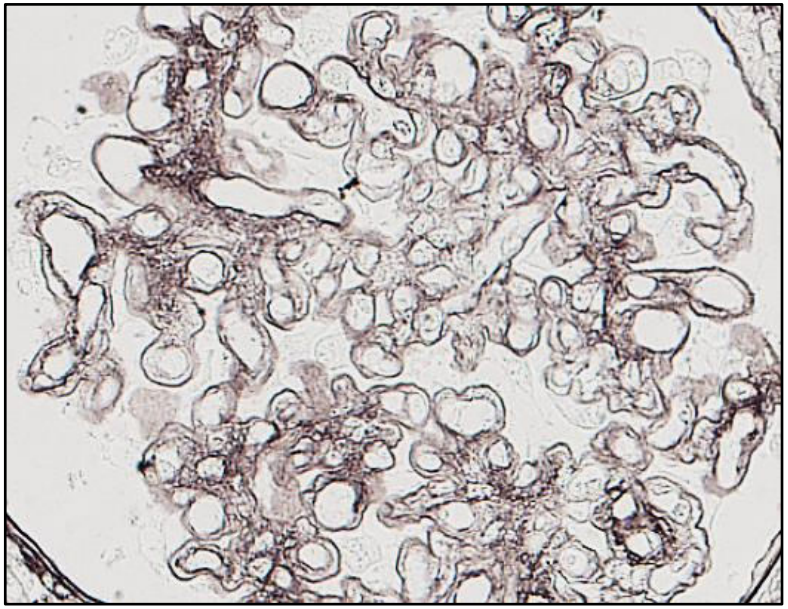
71 y.o. man
with **PMF**

61 y.o. man
with **PMF**





67 y.o. woman
with **PV** and
secondary MF



http://www.kidney-international.org original article
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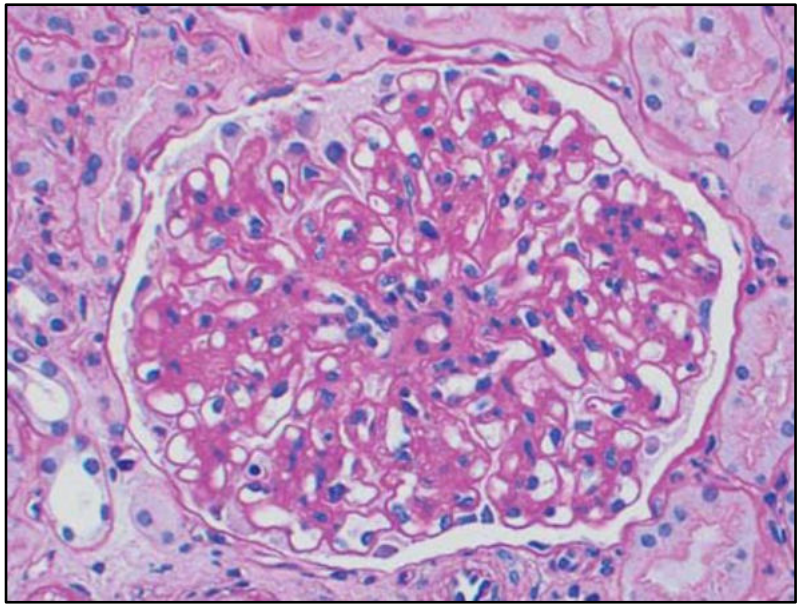
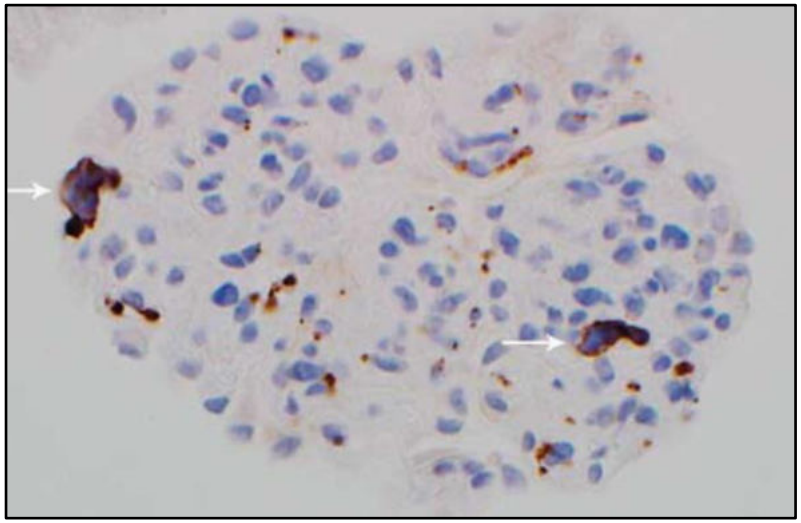
see commentary on page 701

Myeloproliferative neoplasms cause glomerulopathy

Samar M. Said[1], Nelson Leung[2], Sanjeev Sethi[1], Lynn D. Cornell[1], Mary E. Fidler[1], Joseph P. Grande[1], Sandra Herrmann[2], Ayalew Tefferi[3], Vivette D. D'Agati[4] and Samih H. Nasr[1]

Age	Proteinuria (g/24)	S. albumin (g/dl)	Edema	Nephrotic syndrome	Scr (mg/dl)	Type of MPN
64	13	2.8	Yes	Yes	2.2	PMF
87	3.2	3.8	No	No	2.3	PMF
82	14	1.8	Yes	No	5.6	PMF
73	11.8	3	No	No	1.6	PMF
78	7	3	Yes	Yes	4.6	PMF
67	3.4	2.9	No	No	1.5	PMF
72	3.6	2.7	No	No	3.4	PMF
60	7	3	No	No	1.3	PMF
74	3.2	4.5	Yes	No	1	ET
78	6	3.4	Yes	Yes	2.5	CML
68	3	2.3	Yes	Yes	2.2	PV





Said et al. **Kidney Int** 2011

Proposed working definition of MPN-RG

In a patient with MPN:

- ✓ **Mesangial expansion**
- ✓ **Negative immunofluorescence studies**
- ✓ **Mesangial proliferation**
  and/or **glomerular TMA**

3 obligatory criteria

Renal features at diagnosis

In a patient with MPN:

- ✓ **Mesangial expansion**
- ✓ **Negative immunofluorescence studies**
- ✓ **Mesangial proliferation** and/or **glomerular TMA**

3 obligatory criteria

n	**14**
Primary indication for biopsy (%)	
Chronic kidney disease	5 (35.7)
Nephrotic syndrome	4 (28.6)
Acute kidney injury	3 (21.4)
Isolated proteinuria	2 (14.3)
eGFR, mL/min/1.73 m²	39.7 (29.3)
uPCR, g/g	6.0 (4.0)

No added value of intraglomerular hematopoietic cells for diagnosis
(~50% of all patients regardless of renal diagnosis)

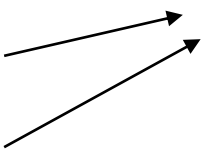
Strong association of MPN-RG with myelofibrosis

In a patient with MPN:

- ✓ **Mesangial expansion**
- ✓ **Negative immunofluorescence studies**
- ✓ **Mesangial proliferation** and/or **glomerular TMA**

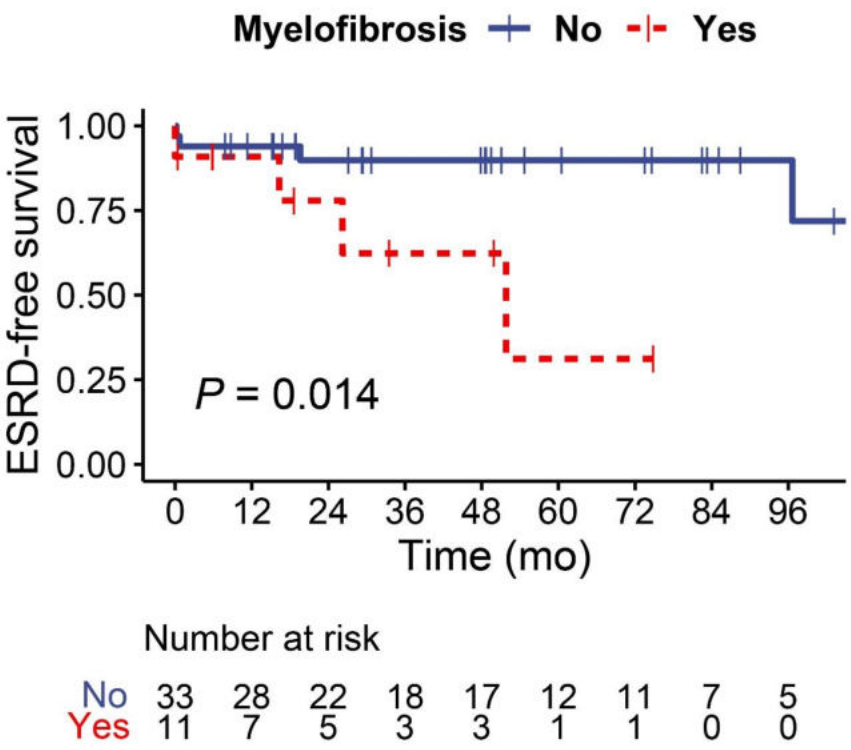
3 obligatory criteria

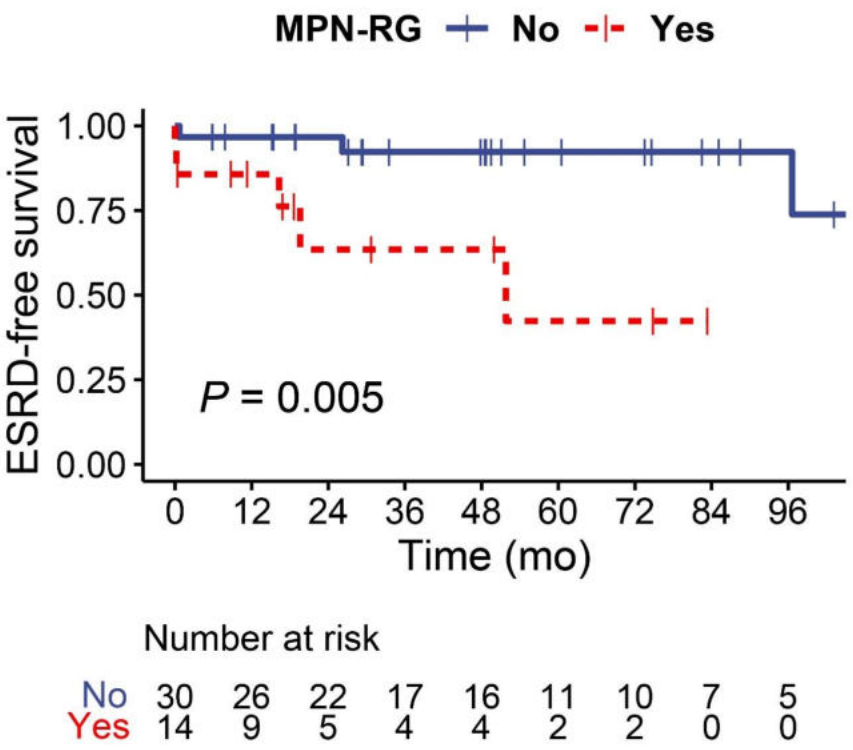
n	**14**
Age, years	65.4 (9.9)
Time since MPN diagnosis, years	9.7 (8.1)
MPN diagnosis (%)	
Chronic myeloid leukemia	3 (21.4)
Polycythemia vera	4 (28.6)
Essential thrombocythemia	3 (21.4)
Primary myelofibrosis	4 (28.6)
Hematological complications (%)	
Secondary myelofibrosis	3 (21.4)
Acute myeloblastic leukemia	1 (7.1)
Acute lymphoblastic leukemia	0 (0.0)



50% had myelofibrosis
(*P* = 0.009)

Death-censored ESRD-free survival





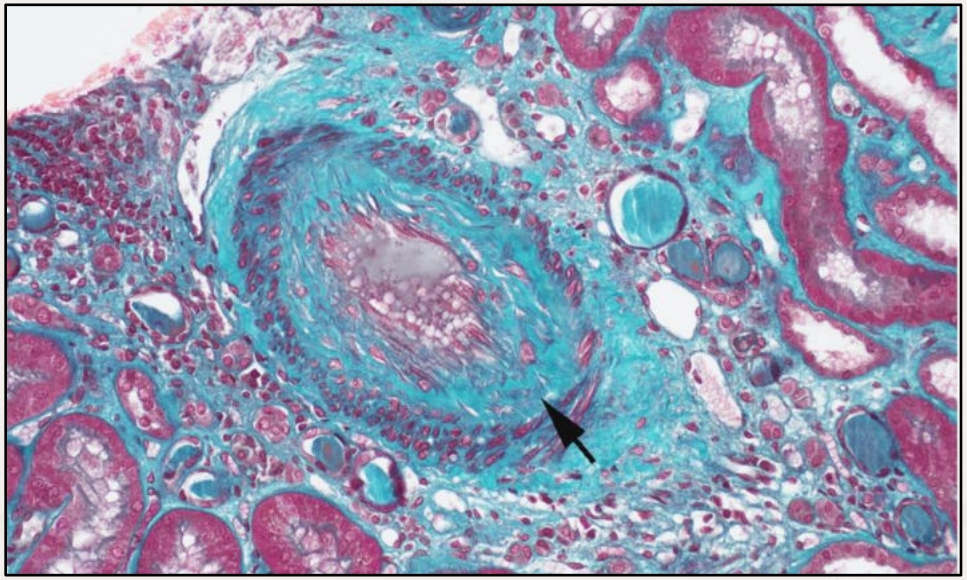
MPN-related glomerulopathy

- Renal insufficiency and **heavy proteinuria** in a MPN patient
- Strong association with **myelofibrosis**

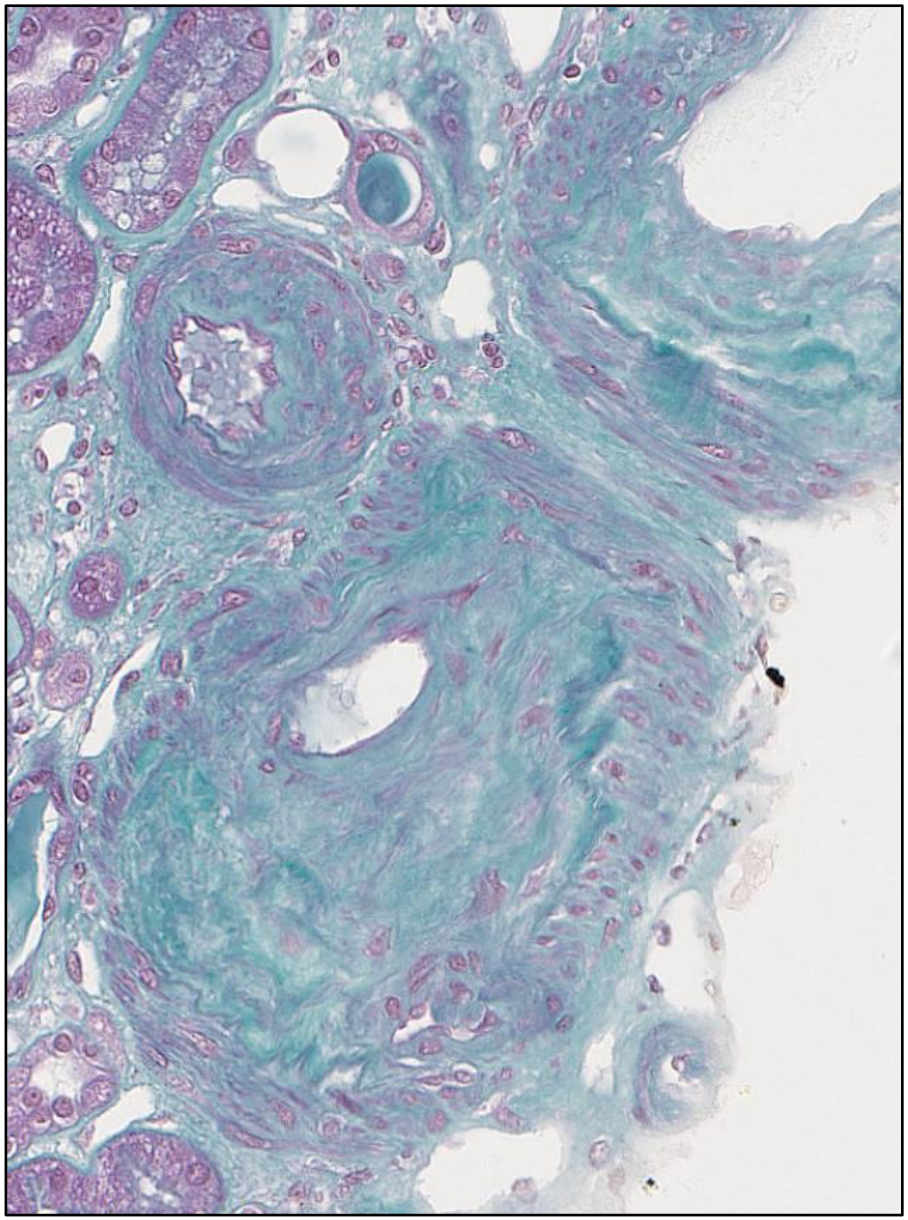
- **Mesangial sclerosis** and **proliferation**, glomerular **TMA**
- Negative immunofluorescence studies
- **No diagnostic value** of intracapillary hematopoietic cells

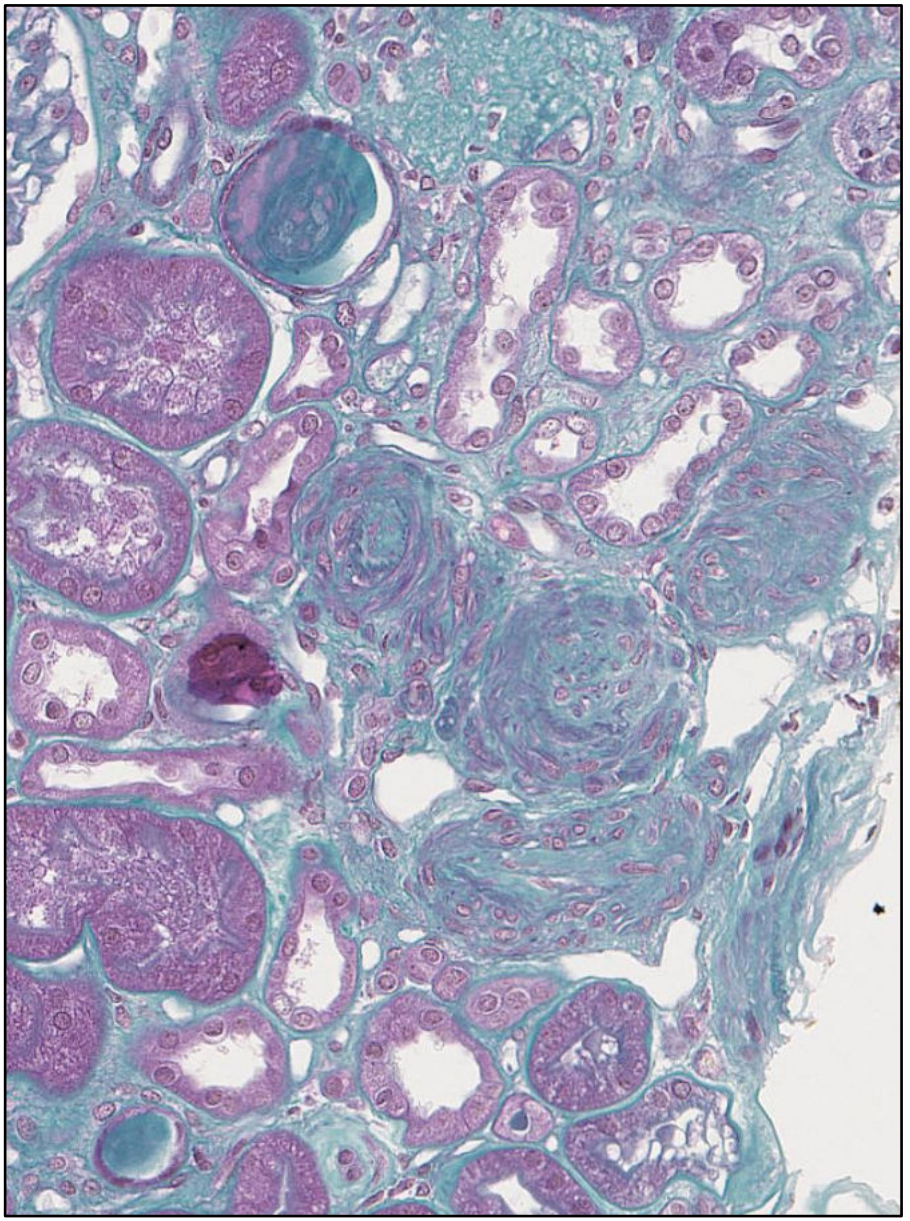
- **Poor renal prognosis**

44 year-old man
with PV & CKD

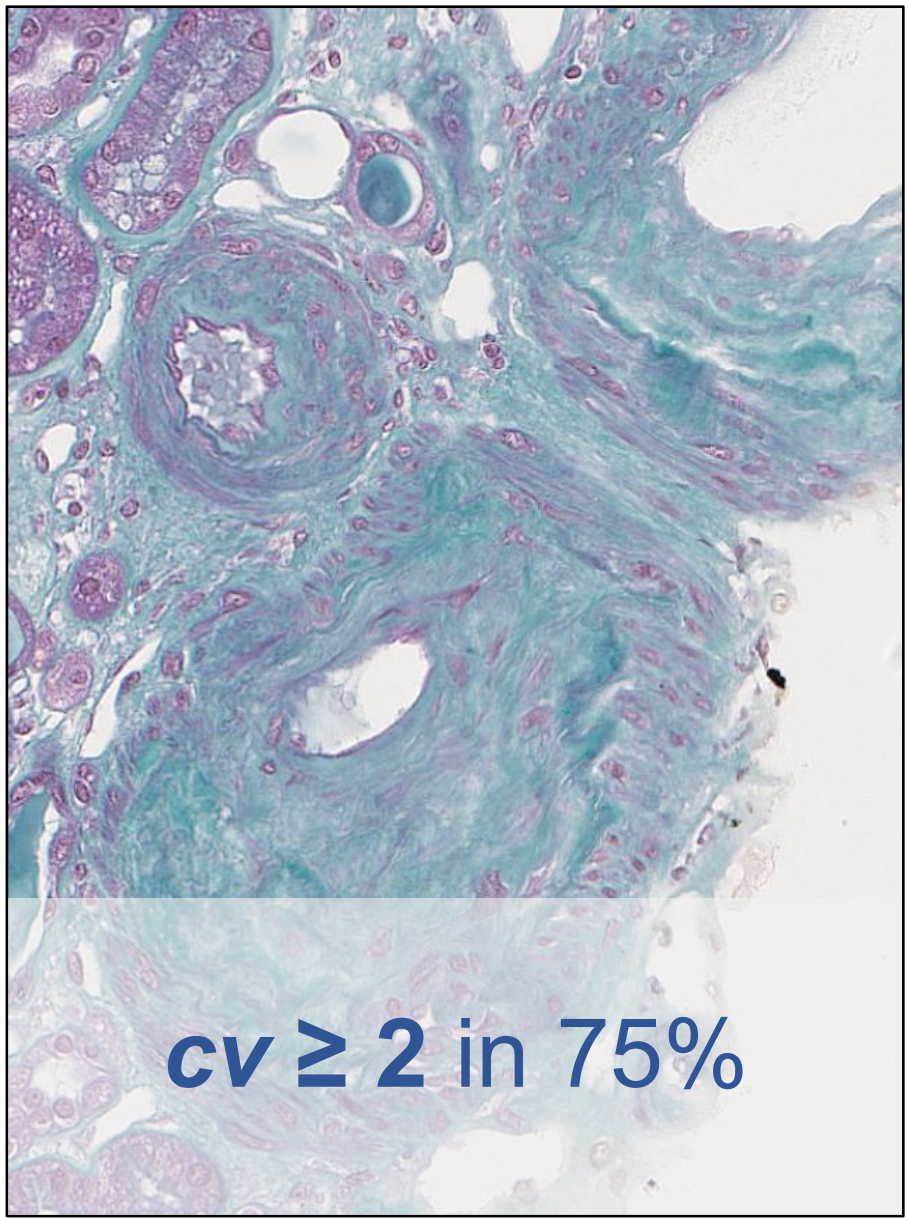


58 year-old woman with ET presenting with AKI

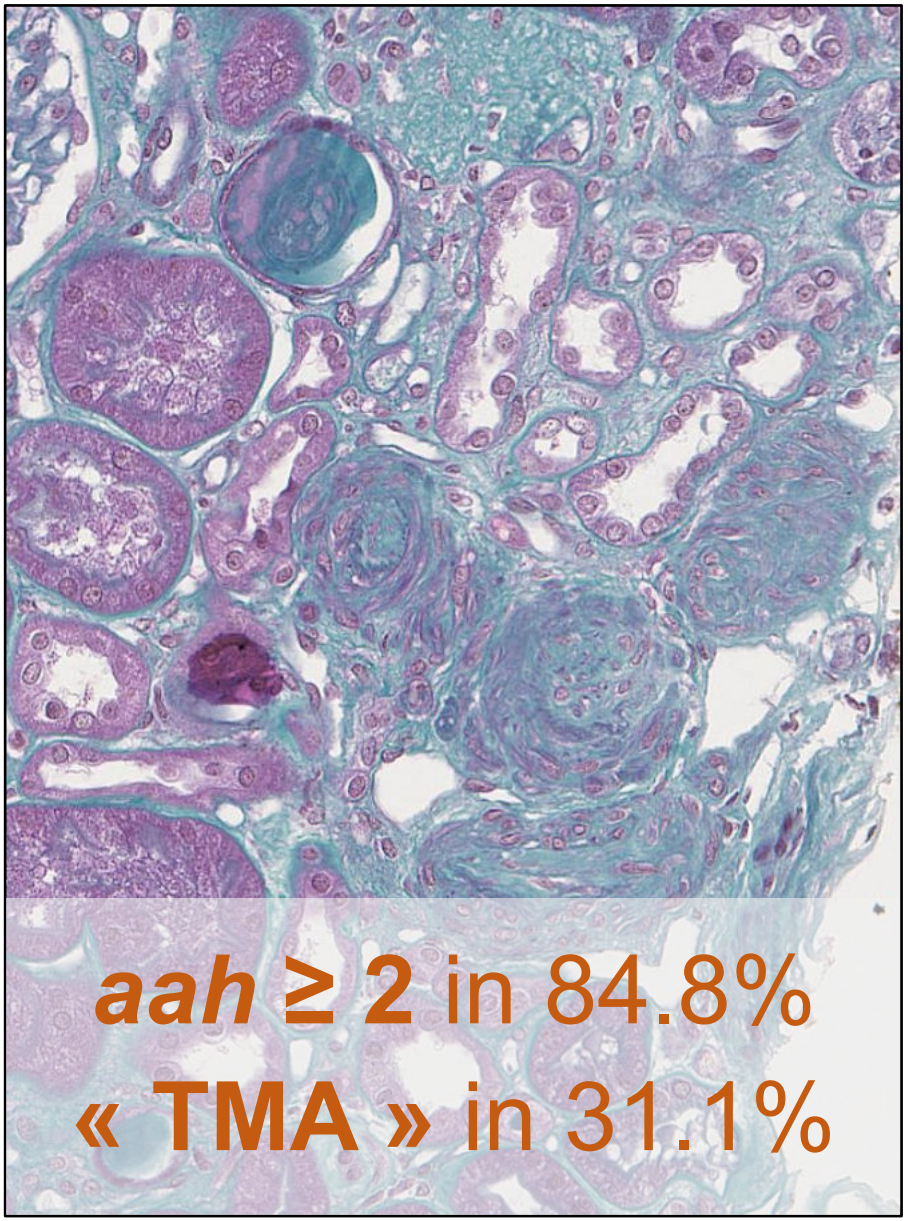




In our MPN biopsy cohort

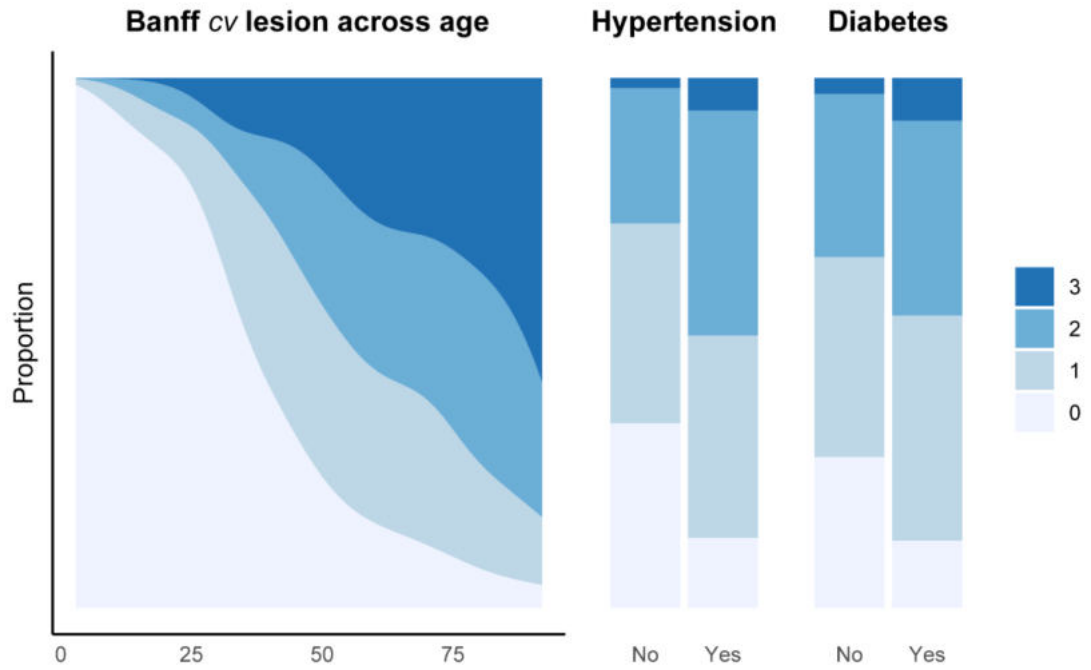


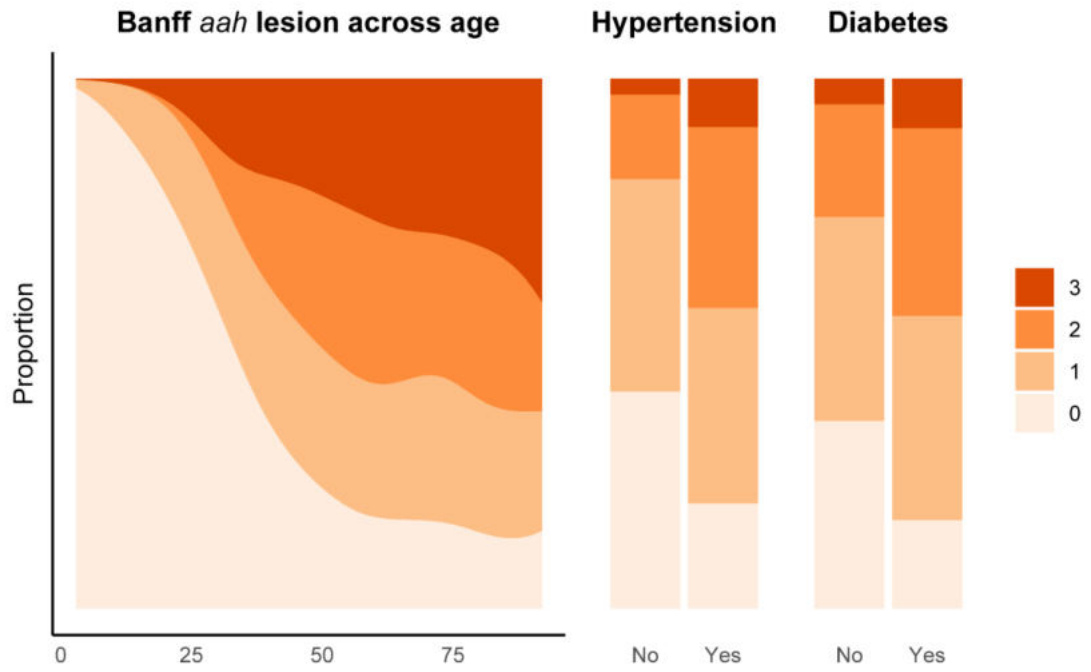
***cv* ≥ 2** in 75%



***aah* ≥ 2** in 84.8%

« TMA » in 31.1%





Intrarenal vessel lesions in the general population

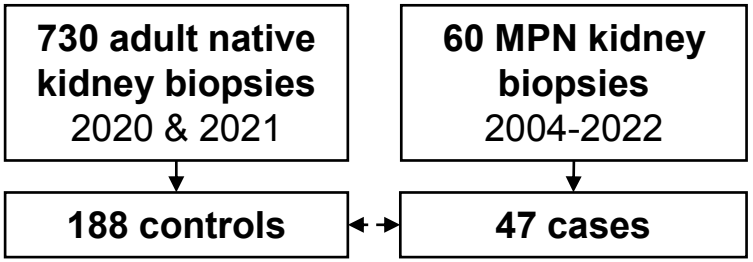
… need for adequate comparison

Brain-dead kidney donors
Day 0 biopsy

Necker transplantation department
(2011-2021)

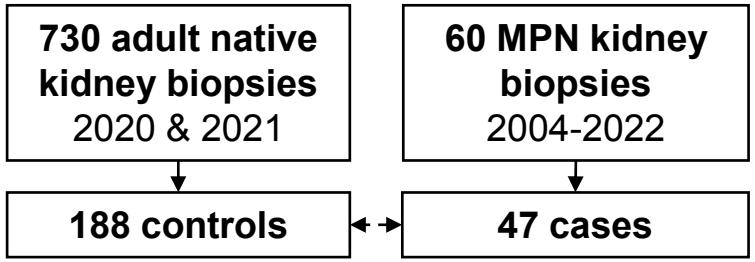
Unpublished

Vascular damage in MPN > control patients



	Controls	MPN
n	188	47
Sex (%)		
Male	120 (63.8)	30 (63.8)
Female	68 (36.2)	17 (36.2)
Age	60.9 (12.0)	60.8 (12.1)
Diabetes (%)	51 (27.1)	14 (29.8)
Hypertension (%)	149 (79.3)	40 (85.1)
Dyslipidemia (%)	84 (44.7)	20 (42.6)
Smoker (%)	102 (58.0)	19 (45.2)
eGFR	42.4 (28.2)	38.2 (25.9)
uPCR	3.1 (4.1)	3.4 (3.8)

Vascular damage in MPN > control patients



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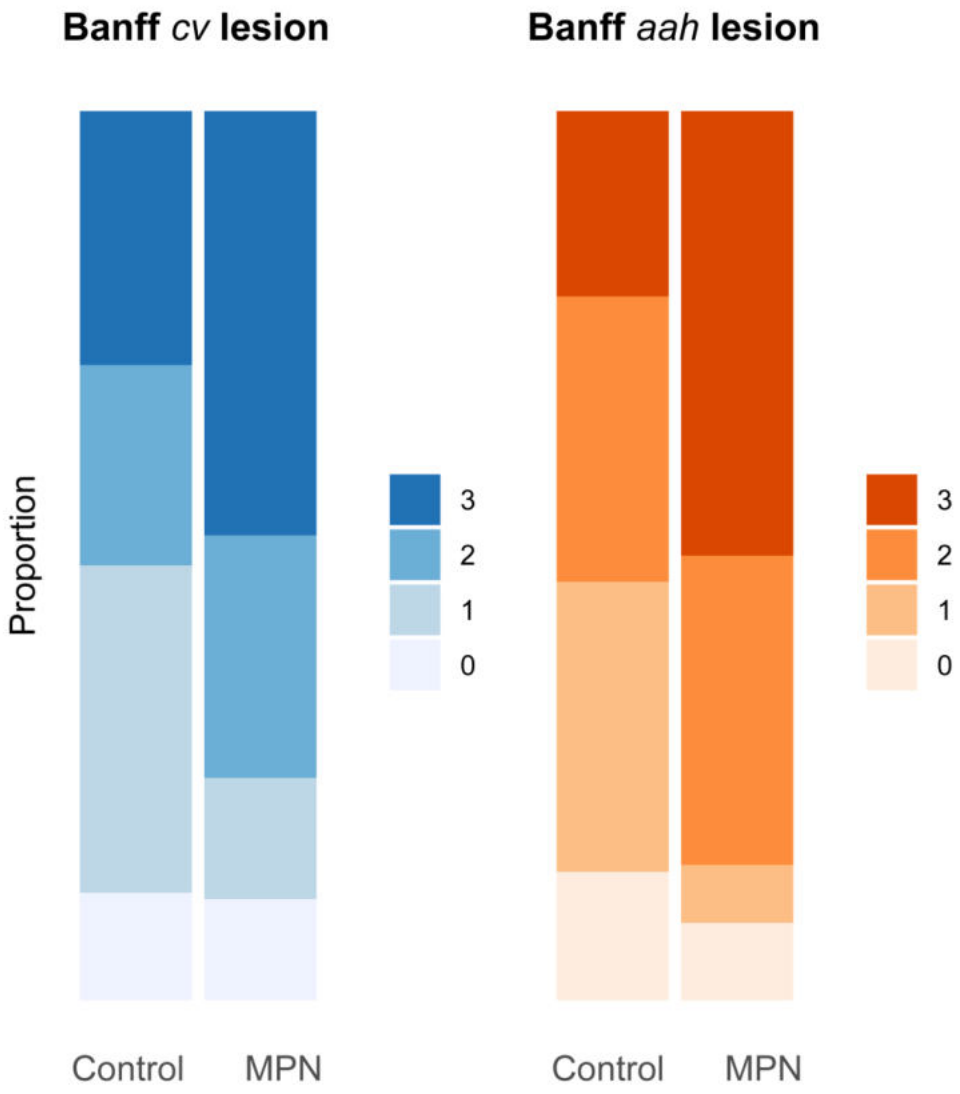

Determinants of *cv* ≥ 2	n	n *cv* 2-3	Univariable OR	Univariable 95% CI	p	Multivariable OR	Multivariable 95% CI	p
Age at kidney biopsy *Per 1 year increment*	226	126	1.044	1.020, 1.069	**<0.001**	1.042	1.018, 1.069	**<0.001**
Myeloproliferative neoplasm					**0.003**			**0.026**
No	182	93	—	—		—	—	
Yes	44	33	**2.871**	1.405, 6.271		**2.427**	1.112, 5.619	
Diabetes mellitus					0.301			0.744
No	164	88	—	—		—	—	
Yes	62	38	1.367	0.757, 2.504		1.117	0.576, 2.188	
Number of antiHTN drugs *Per 1 drug increment*	225	125	1.232	1.016, 1.504	**0.033**	1.116	0.894, 1.397	0.333
Globally sclerotic glomeruli *Per 1% increment*	226	126	1.023	1.010, 1.037	**<0.001**	1.016	1.002, 1.030	**0.027**

Determinants of *aah* ≥ 2	n	n *aah* 2-3	Univariable OR	Univariable 95% CI	p	Multivariable OR	Multivariable 95% CI	p
Age at kidney biopsy *Per 1 year increment*	233	138	1.017	0.995, 1.039	0.138	1.013	0.989, 1.037	0.305
Myeloproliferative neoplasm					**<0.001**			**<0.001**
No	187	99	—	—		—	—	
Yes	46	39	**4.952**	2.229, 12.60		**4.446**	1.892, 11.81	
Diabetes mellitus					**0.001**			**0.041**
No	168	89	—	—		—	—	
Yes	65	49	2.718	1.458, 5.285		2.040	1.029, 4.169	
Number of antiHTN drugs *Per 1 drug increment*	232	137	1.576	1.280, 1.969	**<0.001**	1.430	1.134, 1.824	**0.002**
Globally sclerotic glomeruli *Per 1% increment*	233	138	1.021	1.009, 1.035	**<0.001**	1.009	0.996, 1.024	0.188

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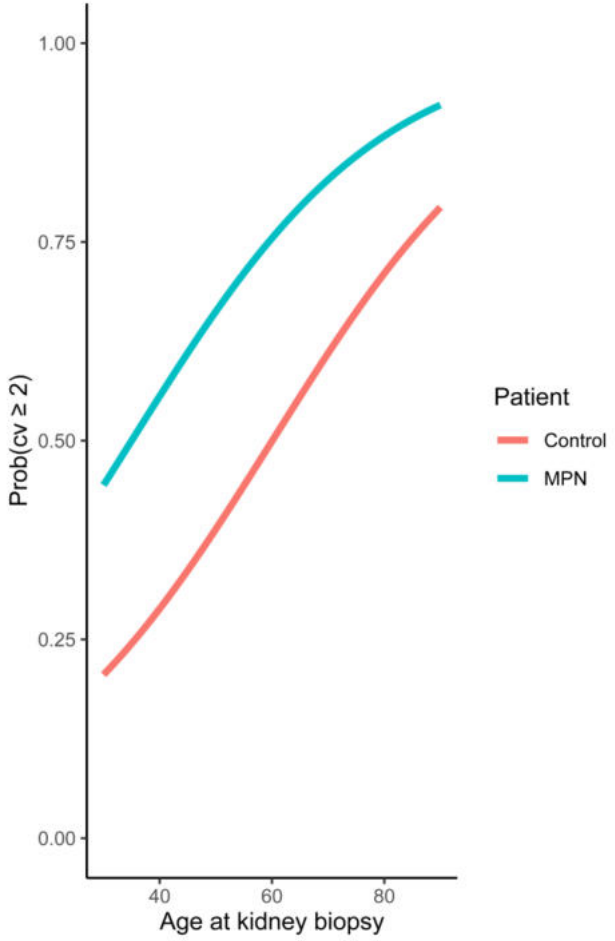
MPN-related vascular nephrosclerosis

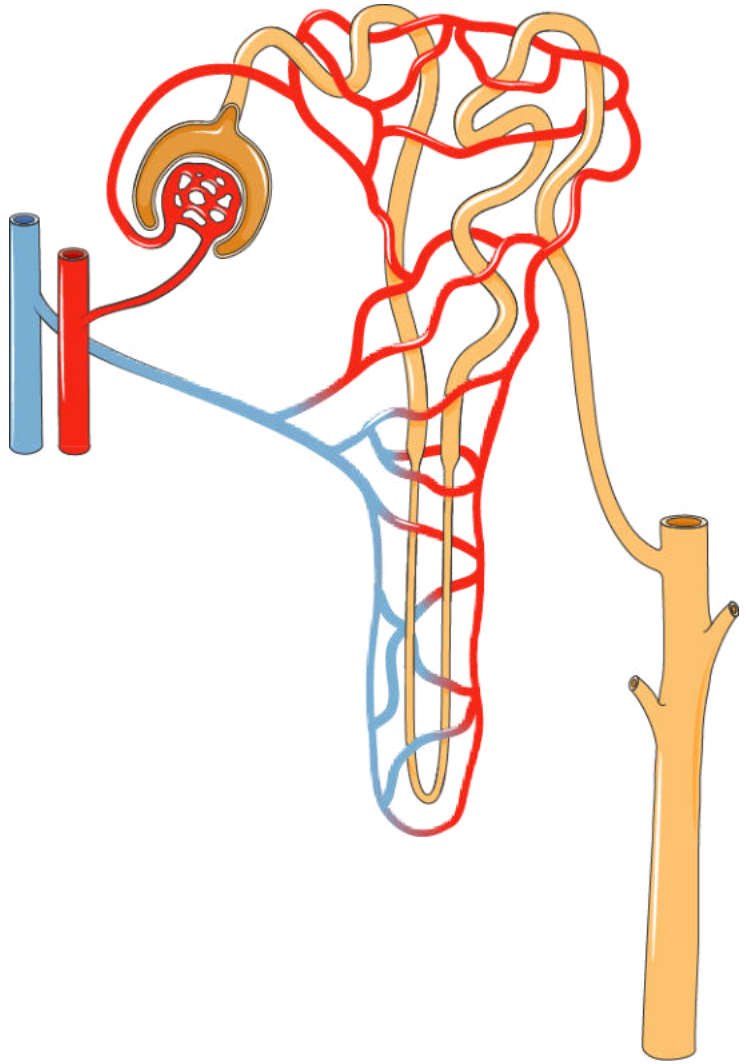
- Acute features such as arteriolar TMA

- **Mostly chronic vessel scarring**
  - **Arteriolar hyalinosis** (*aah*)
  - **Arteriosclerosis** (*cv*)

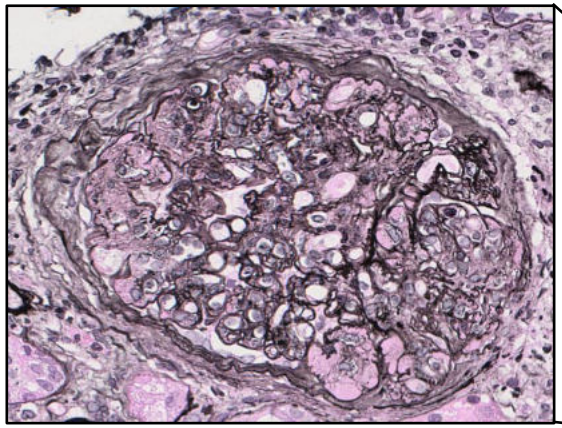
- **Occurring independently of traditional risk factors**



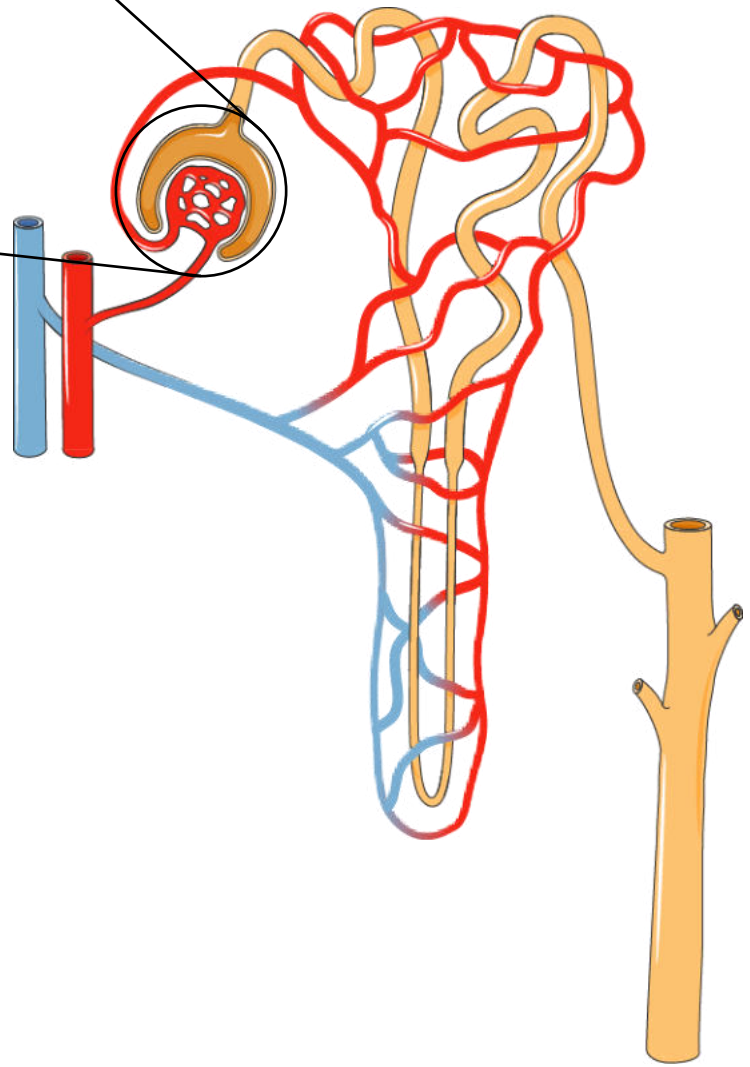
Renal pathology in MPN patients



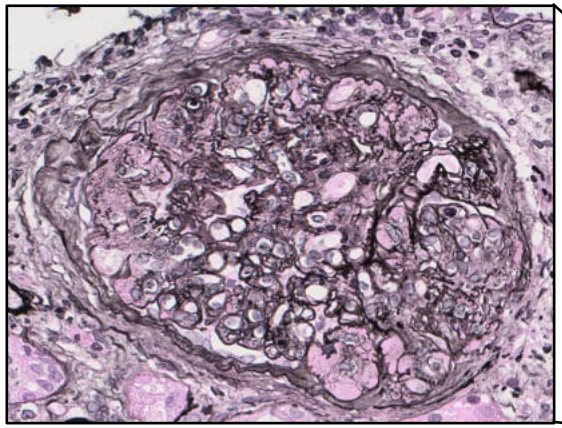
Renal pathology in MPN patients



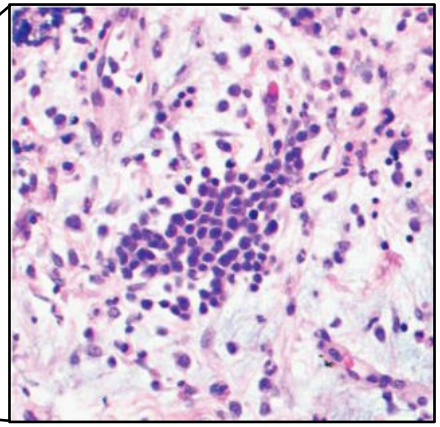
MPN-related glomerulopathy



Renal pathology in MPN patients

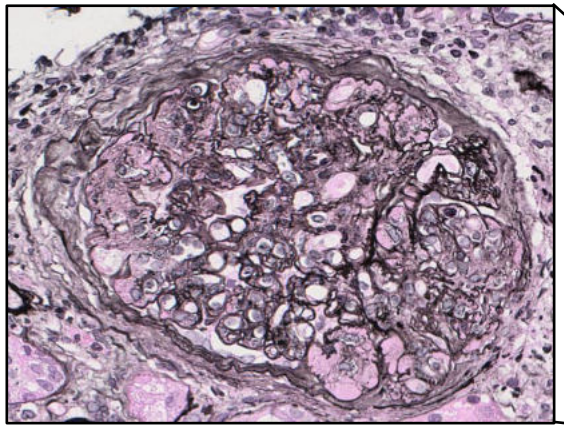


MPN-related glomerulopathy

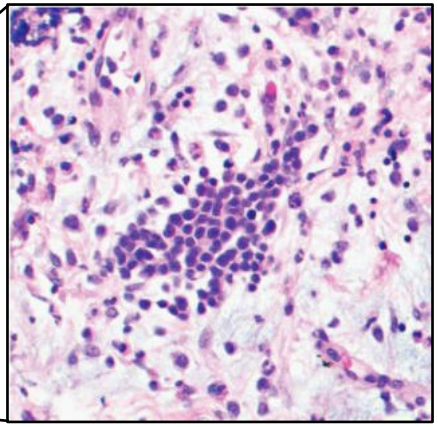


Intrarenal hematopoiesis

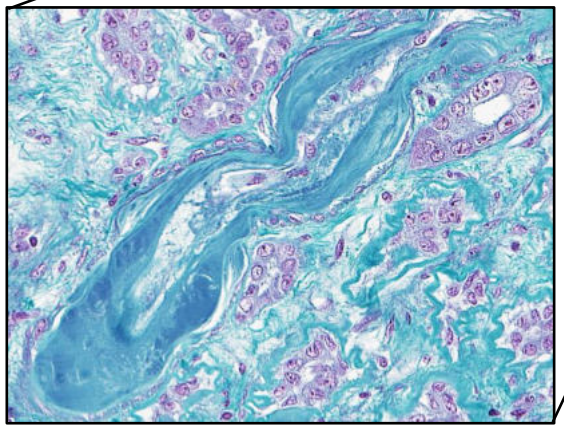
Renal pathology in MPN patients



MPN-related glomerulopathy

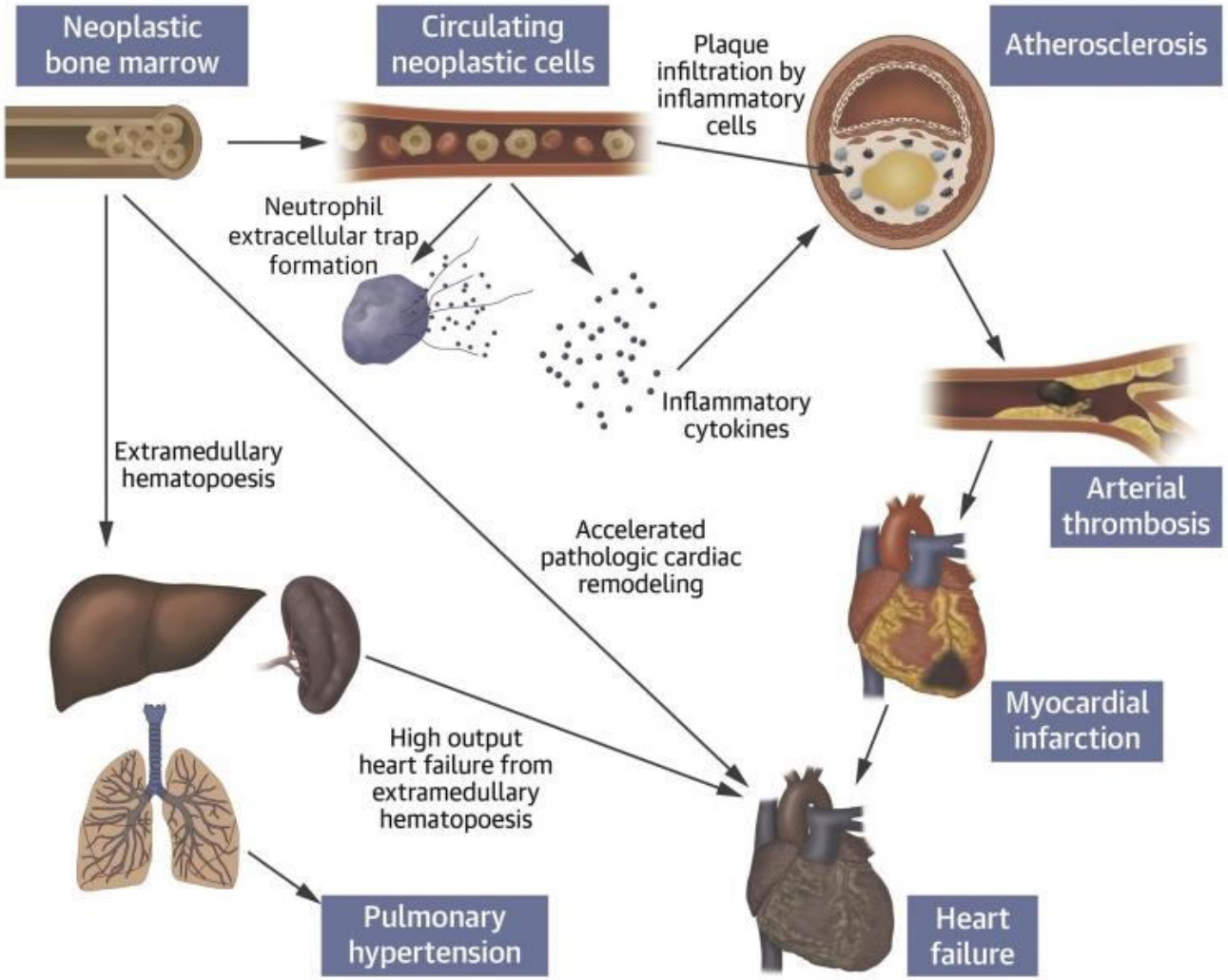


Intrarenal hematopoiesis



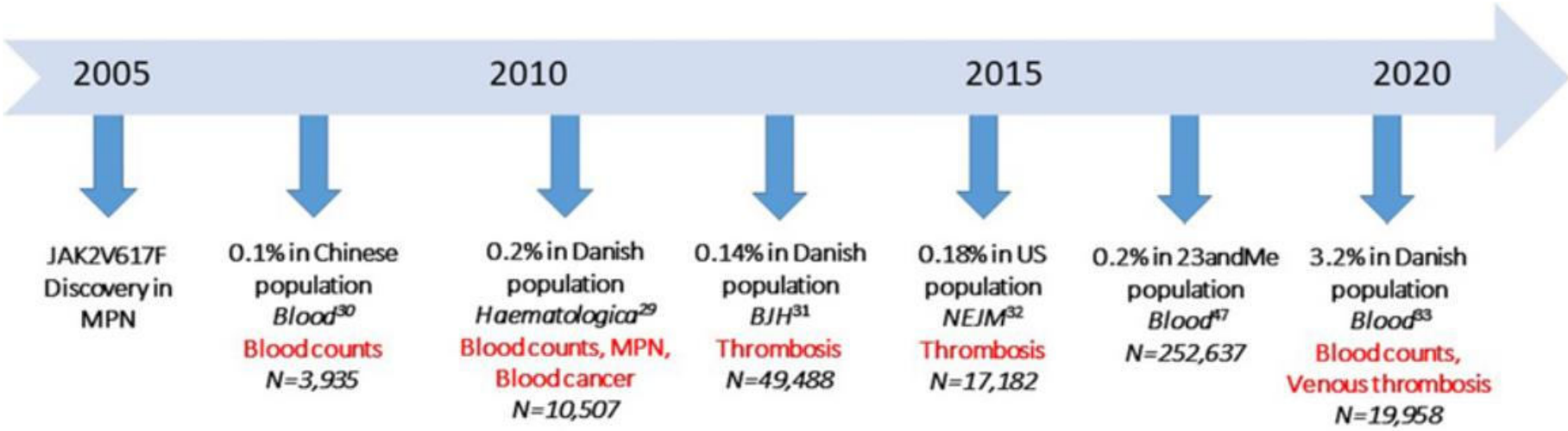
MPN-related
vascular nephrosclerosis

Kidney as a target of MPN-associated vasculopathy



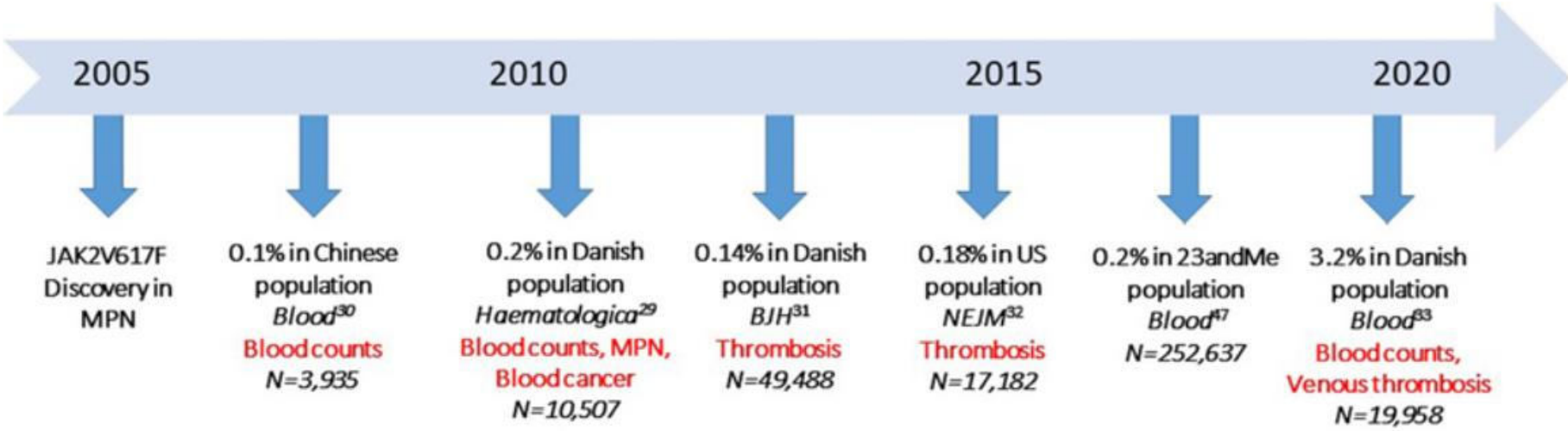
Leiva O et al. **J Am Coll Cardiol CardioOnc** 2022

Kidney as a target of MPN-associated vasculopathy



Moliterno & Kaizer **Blood** 2020 ; Goforth et al. **Kidney International** 2006

Kidney as a target of MPN-associated vasculopathy



http://www.kidney-international.org original article

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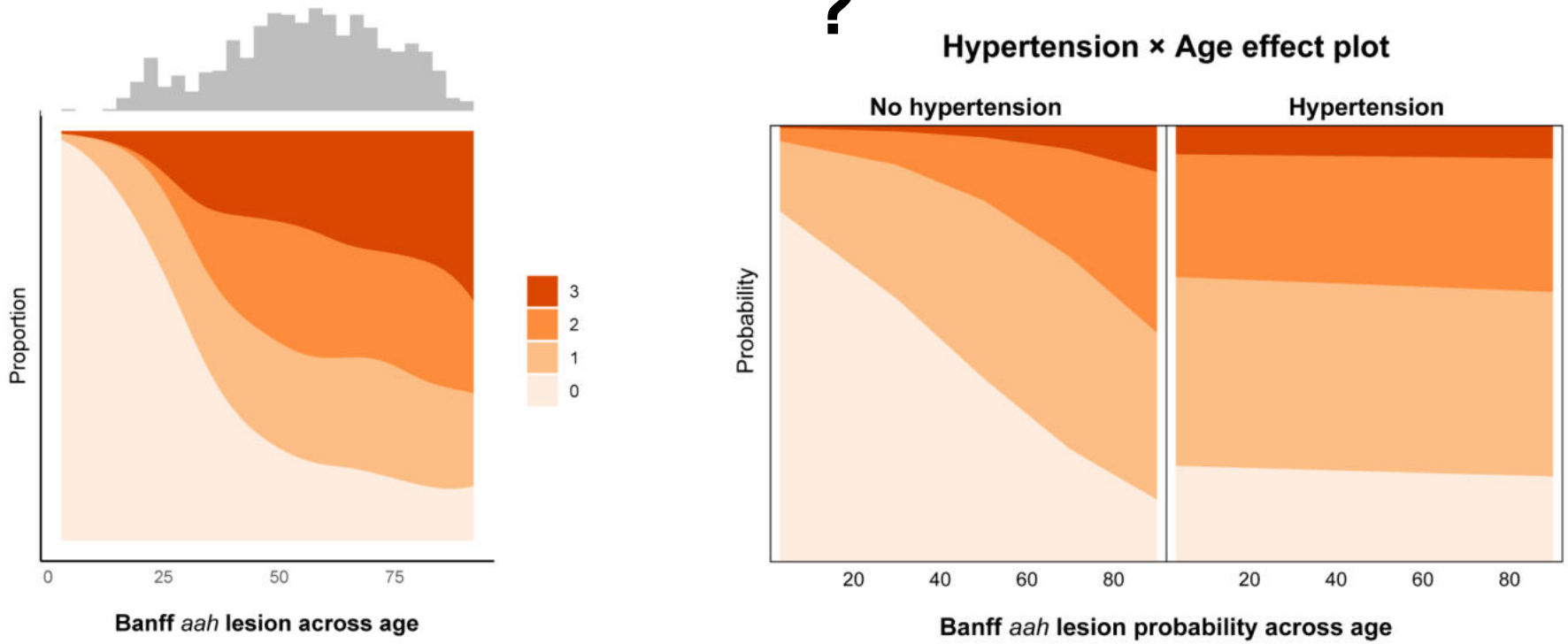
Renal vascular sclerosis is associated with inherited thrombophilias

Moliterno & Kaizer **Blood** 2020 ; Goforth et al. **Kidney International** 2006

« Hypertensive » nephrosclerosis

Hypertension ⇄ **CKD**

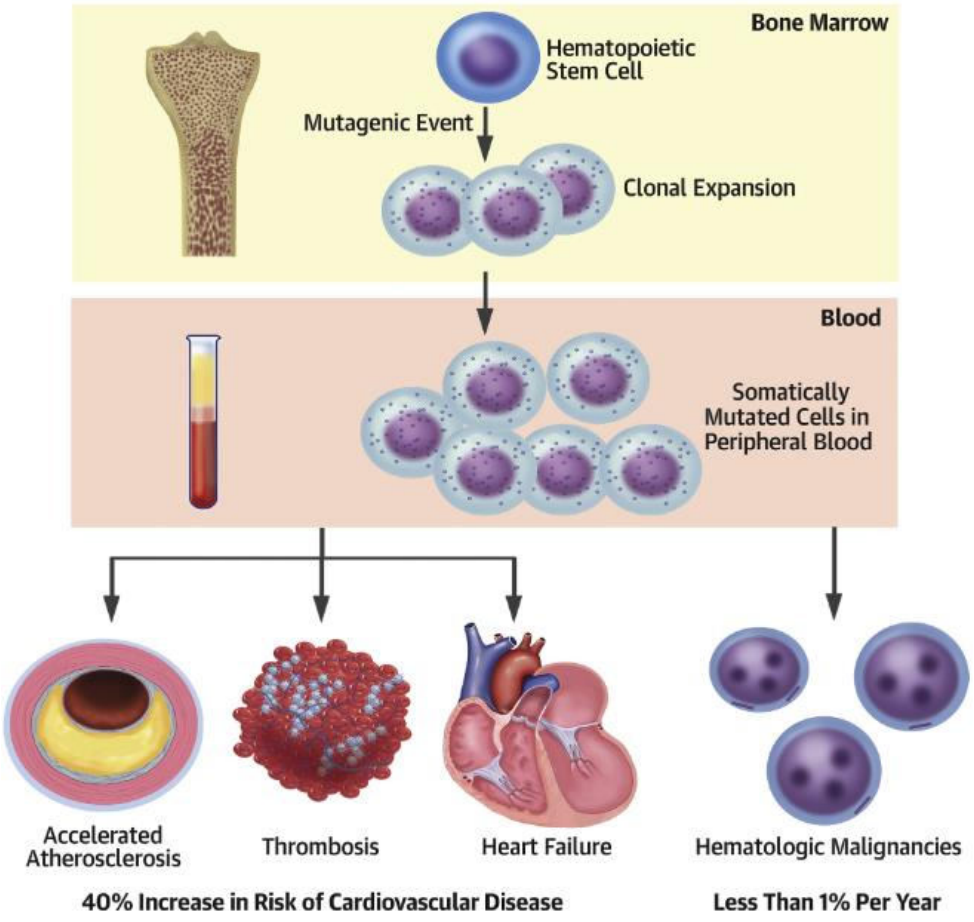
?

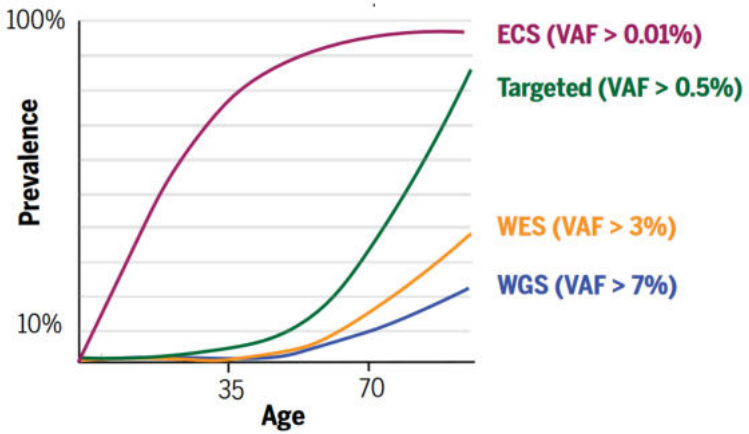


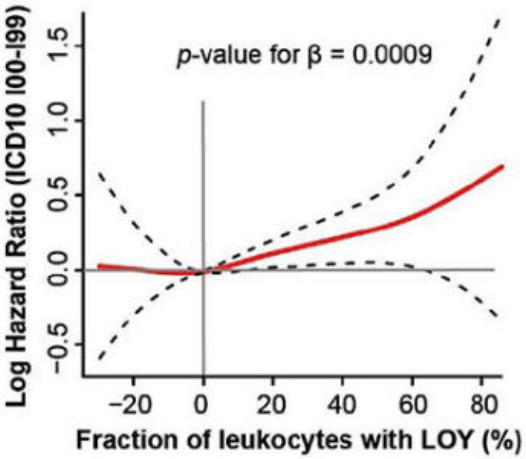
Ordinal regression model for *aah* score on Day 0 biopsy (brain-dead kidney donors), adjusted for age, sex, hypertension, smoking, umbilical perimeter, glomerulosclerosis.
Necker transplantation department (2011-2021)

Unpublished

Clonal hematopoiesis of indeterminate prognosis

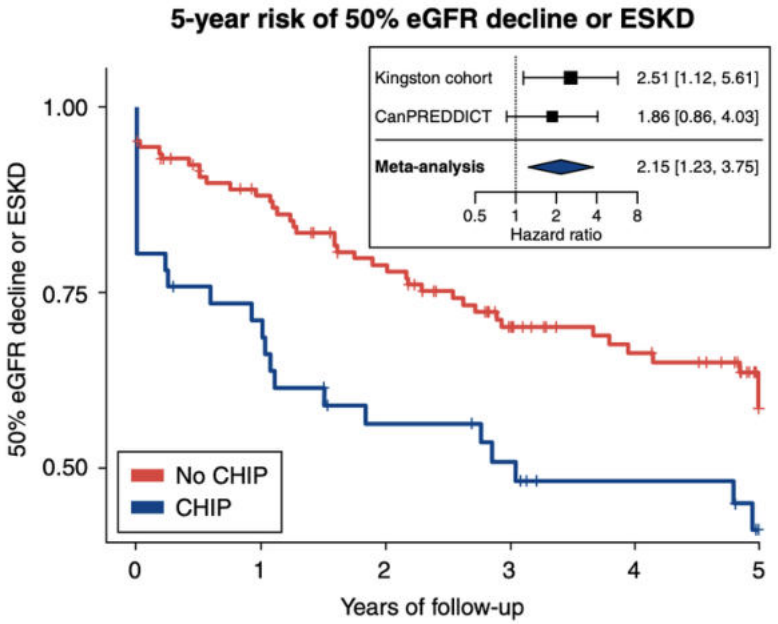






Libby et al. **J Am Coll Cardiol** 2019 ; Jaiswal & Ebert **Science** 2019 ; Sano et al. **Science** 2022

CHIP-associated vascular nephrosclerosis ?



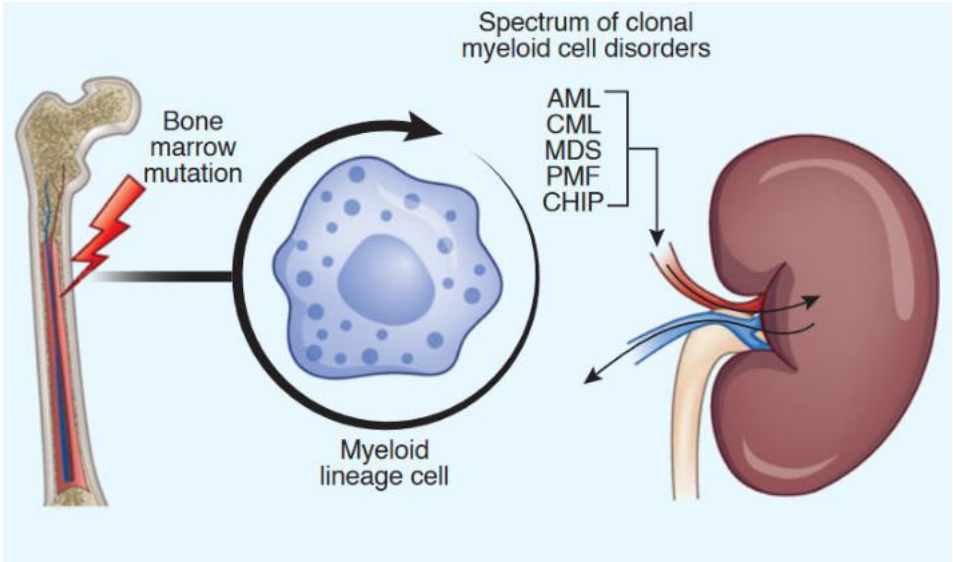


Table 2. Associations of Clonal Hematopoiesis of Indeterminate Potential with 30% Decline in eGFR

	CHIP	No. of Participants	No. of eGFRs[a]	FU Time, y[a]	No. of Events	Incidence per 100 PY	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[b]
ARIC	Yes	584	3 [3-4]	9 [8-22]	143	2.20	1.23 (1.04-1.46)	1.20 (1.01-1.43)
	No	5,991	3 [3-4]	9 [8-23]	1,392	1.94	1.00 (reference)	1.00 (reference)
CHS	Yes	240	3 [2-3]	7 [3-7]	40	2.14	1.48 (1.02-2.13)	1.38 (0.92-2.06)
	No	1,461	3 [2-3]	7 [4-7]	216	1.53	1.00 (reference)	1.00 (reference)
MESA	Yes	178	4 [4-4]	9 [9-10]	22	1.44	0.99 (0.64-1.52)	0.85 (0.55-1.30)
	No	3,550	4 [4-4]	9 [9-10]	433	1.39	1.00 (reference)	1.00 (reference)
Meta-analysis	Yes	1,002	3 [3-4]	8 [7-14]	205	2.05	1.24 (1.07-1.43)[c]	1.17 (1.01-1.36)[d]
	No	11,002	3 [3-4]	8 [7-15]	2,041	1.71	1.00 (reference)	1.00 (reference)

Vlasschaert et al. **J Am Soc Nephrol** 2022
Vlasschaert et al. **CJASN** 2022 ; Kestenbaum et al. **Am J Kidney Dis** 2023

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Néphrologie Pontoise
Dr Charlotte Jouzel

Néphrologie Mayotte
Dr Sarah Permal

Cardiovascular disease in MPN patients

History of thrombosis (%)	22 (46.8)
Venous thromboembolism (%)	11 (23.4)
Ischemic stroke (%)	8 (17.0)
Toe necrosis (%)	4 (8.5)
Myocardial infarction (%)	3 (6.4)
Medullary infarction (%)	1 (2.1)
Acute limb ischemia (%)	1 (2.1)
Splenic infarction (%)	1 (2.1)
Acute mesenteric ischemia (%)	1 (2.1)
Chronic vascular disease (%)	15 (31.9)
Chronic limb ischemia (%)	5 (10.6)
Chronic ischemic heart disease (%)	4 (8.5)
Pulmonary hypertension (%)	3 (6.4)
Raynaud's phenomenon (%)	2 (4.3)
Erythromelalgia (%)	1 (2.1)
Livedo (%)	1 (2.1)
Nodular regenerative hyperplasia (%)	1 (2.1)
History of carotid endarterectomy (%)	1 (2.1)
Osteonecrosis of the femoral head (%)	1 (2.1)
Diffuse unexplained aneurysmal disease (%)	1 (2.1)

Hematological features

Treatments

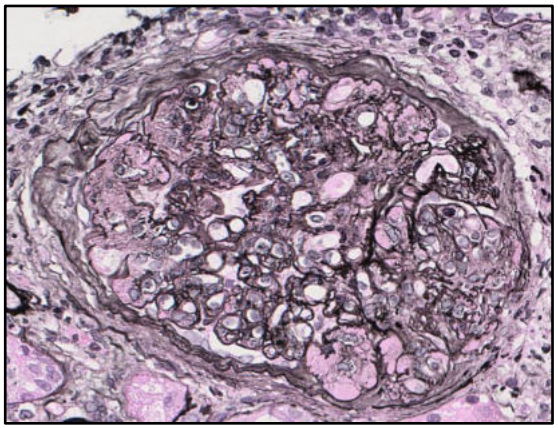
TKIs (%)	16 (34.0)
Imatinib (%)	16 (34.0)
Dasatinib (%)	10 (21.3)
Nilotinib (%)	4 (8.5)
Bosutinib (%)	1 (2.1)
Ponatinib (%)	0 (0.0)
IFNα (%)	7 (14.9)
Ruxolitinib (%)	7 (14.9)
Hydroxyurea (%)	28 (59.6)
Anagrelide (%)	4 (8.5)
HSCT (%)	3 (6.4)

Biology

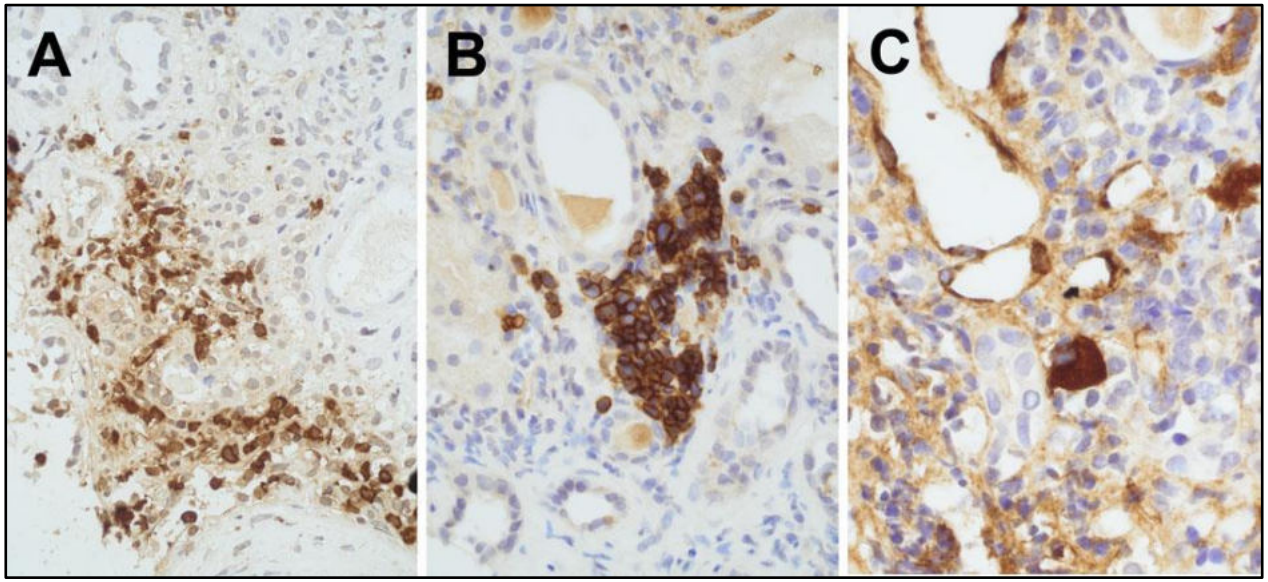
Hemoglobin, g/dL	11.76 (2.4)
Leucocytes, G/L	10.7 (11.0)
Platelets, G/L	295.0 (178.0)
CRP, mg/L	10.5 (17.7)
Uric acid, µmol/L	470.6 (145.9)
LDH, UI/L	559.5 (473.5)

Immunohistochemistry results

IHC+ in glomerular capillaries (%)	23 (56.1)
GPC-positive cells (%)	1 (2.4)
MPO-positive cells (%)	23 (56.1)
FVIII-positive cells (%)	0 (0.0)
IHC+ in peritubular capillaries (%)	19 (43.2)
GPC-positive cells (%)	2 (4.5)
MPO-positive cells (%)	19 (43.2)
FVIII-positive cells (%)	1 (2.3)
IHC+ in interstitium (%)	11 (25.0)
GPC-positive cells (%)	1 (2.3)
MPO-positive cells (%)	11 (25.0)
FVIII-positive cells (%)	1 (2.3)



Renal extramedullary hematopoiesis and concomitant glomerulopathy in a 70 year-old man with PMF



Significance of IHC positivity in glomeruli

	Negative IHC	Positive IHC	*P*
n	**18**	**23**	
Sclerotic glomeruli, %	37.8 (20.2)	40.6 (23.4)	0.833
Segmental sclerosis (%)	11 (61.1)	18 (78.3)	0.307
Mesangial expansion (%)	7 (38.9)	11 (50.0)	0.537
Mesangial hypercellularity (%)	9 (50.0)	10 (45.5)	1.000
Glomerular TMA (%)	1 (5.9)	6 (27.3)	0.113
MPN-related glomerulopathy (%)	7 (38.9)	6 (27.3)	0.659
Proteinuria/creatininuria ratio, g/g	4.04 (4.46)	3.11 (3.61)	0.474
Blood leukocytes count, G/L	**7.02 (3.84)**	**14.81 (14.74)**	**0.036**
Positive IHC in peritubular capillaries (%)	**2 (11.1)**	**17 (73.9)**	**<0.001**

Positive glomerular IHC in patients with
acute tubulointerstitial nephritis, oxalate nephropathy,
diabetic kidney disease, …

Vascular disease in MPN patients

Arteriolar hyalinosis (*aah*) (%)	
0	4 (8.7)
1	3 (6.5)
2	16 (34.8)
3	23 (50.0)
Other arteriolar lesions	
Fibrous arteriolar occlusion (%)	6 (13.3)
Arteriolar thrombosis (%)	1 (2.2)
Arteriolar mucoid intimal thickening (%)	8 (17.8)
Arteriolar myocyte vacuolization (%)	5 (11.1)
Arterial intimal fibrosis (*cv*) (%)	
0	5 (11.4)
1	6 (13.6)
2	12 (27.3)
3	21 (47.7)
Other arterial lesions	
Arterial media hypertrophy (%)	12 (28.6)
Fibrous arterial occlusion (%)	2 (4.8)
Arterial thrombosis (%)	0 (0.0)
Arterial mucoid intimal thickening (%)	2 (4.8)
Focal cortical atrophy (%)	5 (11.4)
Tubular pseudothyroidization (%)	12 (27.3)
Tubular pseudoendocrinization (%)	10 (22.7)