La biopsie rénale dans le cadre des vascularites associées aux ANCA

2nde journée de formation organisée par le GFEV
le 08 novembre 2024
à la faculté de médecine de Necker

Indications PBR dans AAV

Diagnostic

PBR : « gold standard » pour diagnostic GN

Recommandée par EULAR dans AAV *Yates Ann Rheum Dis. 2016*

PBR non systématique dans AAV

présentation classique = GNRP

forte suspicion clinique et biologie

étude RAVE : PBR réalisée dans 48% des cas *Pearce Rheumatolgy 2015*

Présentation moins brutale : hématurie et dégradation plus lente fonction rénale

VPP des ANCA : 35% => cancer, infections, médicaments *Bossuyt Nat Rev Rheumatology 2017*

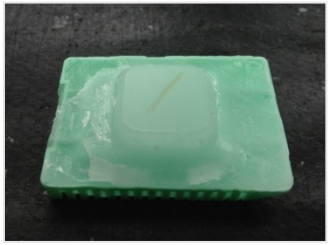
Pronostic

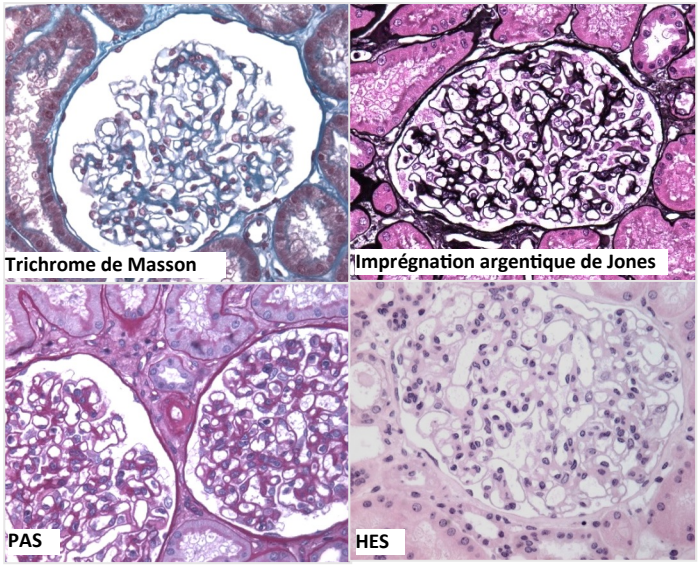
Etat des lieux des lésions actives et des lésions chroniques

Aide au choix thérapeutique ?

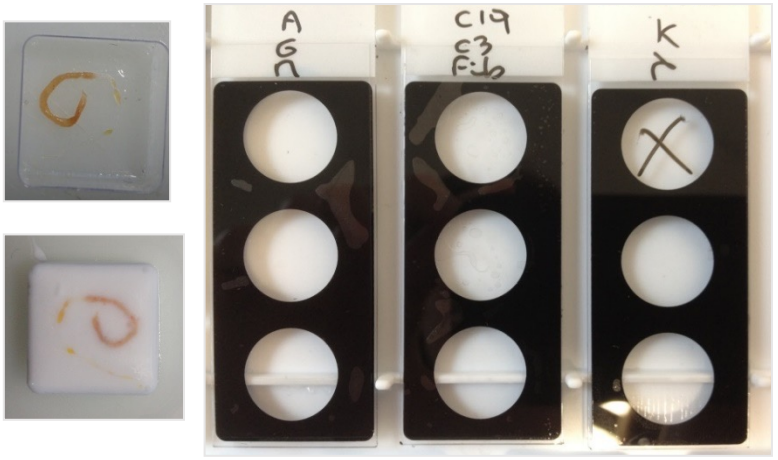
PBR : modalités de prélèvement et aspects technique

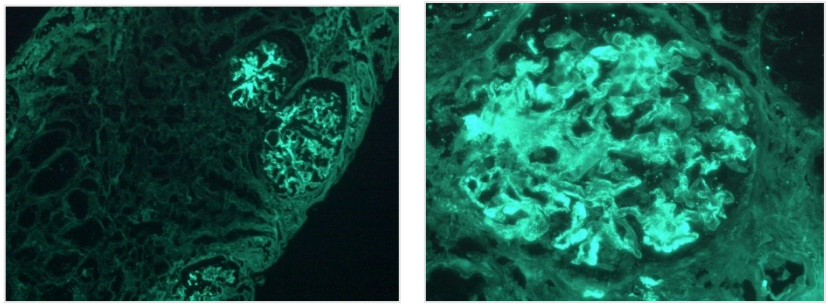
1 biopsie : Fixation A.F.A. : 1 à 3h
Inclusion en paraffine
Coupes de 2 à 3 µm
Colorations spéciales





1 biopsie : Congélation
Immunofluorescence :
dépôts d'Ig ou de complément





1 biopsie : +/- M.E. (glutaraldéhyde)

AAV : description histopathologique

GNEC : glomérulonéphrite nécrosante à croissants

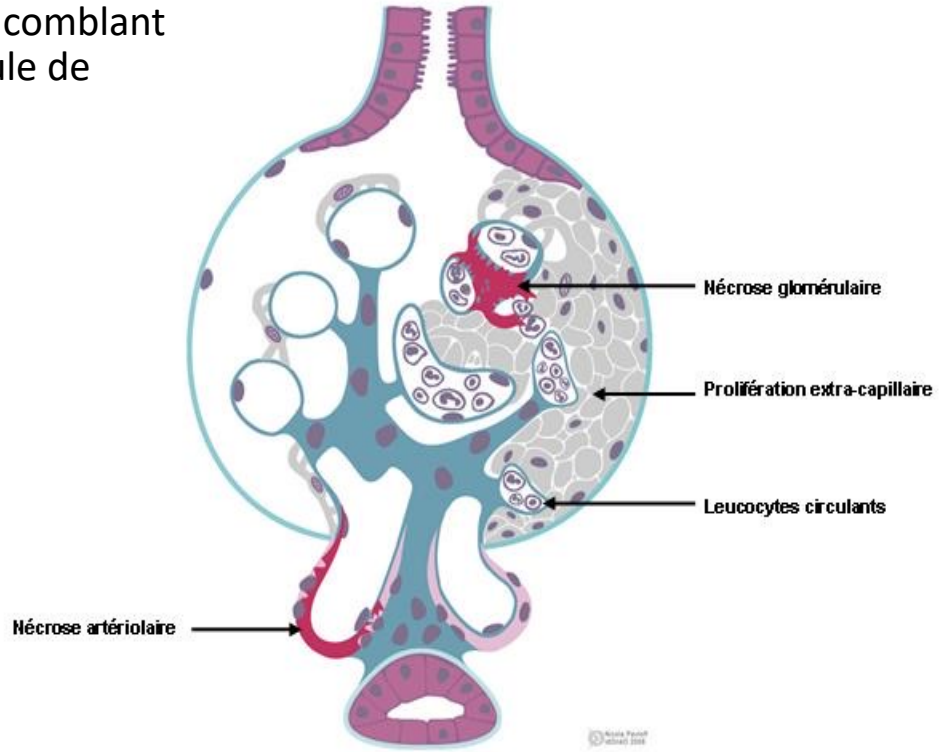
Croissant : ≥ 2 couches cellulaires extra-capillaires comblant ≥ 1/3 la chambre urinaire et au contact de la capsule de Bowman

Nécrose du capillaire glomérulaire

Afflux de cellules inflammatoires

Cylindres hématiques

Infiltrat inflammatoire interstitiel abondant



Noel LH. Mehrenberger M. Diagnos/ardans

AAV : description histopathologique

Perte de l'intégrité du capillaire glomérulaire

fuite de protéine plasmatiques dans la chambre urinaire
thrombine, cytokines => prolifération des cellules épithéliales
afflux de monocytes/macrophages

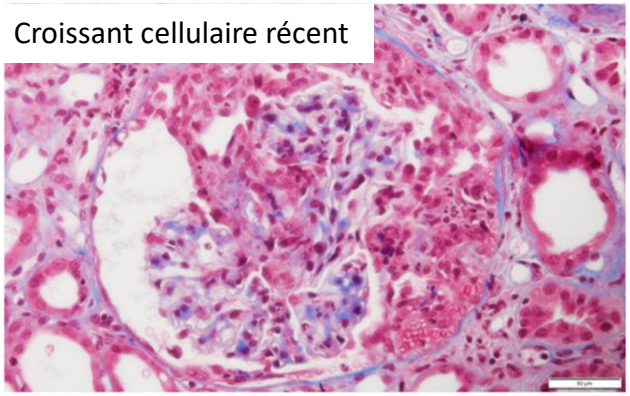
Composition du croissant variable selon l'âge du croissant

cellules épithéliales
monocytes/macrophages
synthèse de collagène par cellules épithéliales, fibroblastes
apoptose des cellules épithéliales

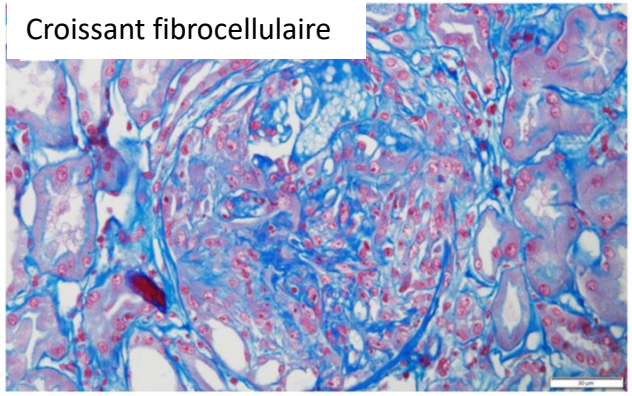
Croissant cellulaire > 90% cellules
Croissant fibreux <10% cellules
Croissant fibro cellulaire

Lésions d'âges différents : évolution par poussée AAV

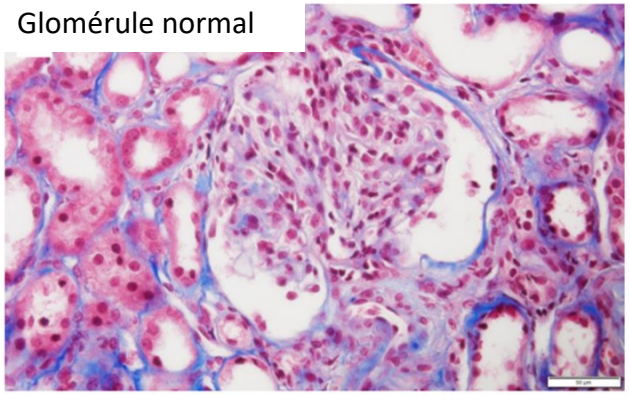
Croissant cellulaire récent



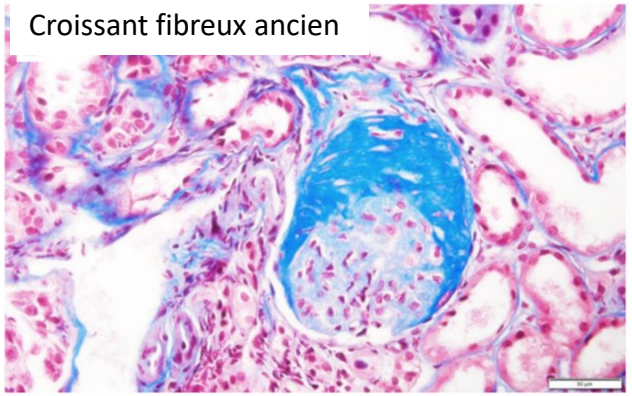
Croissant fibrocellulaire



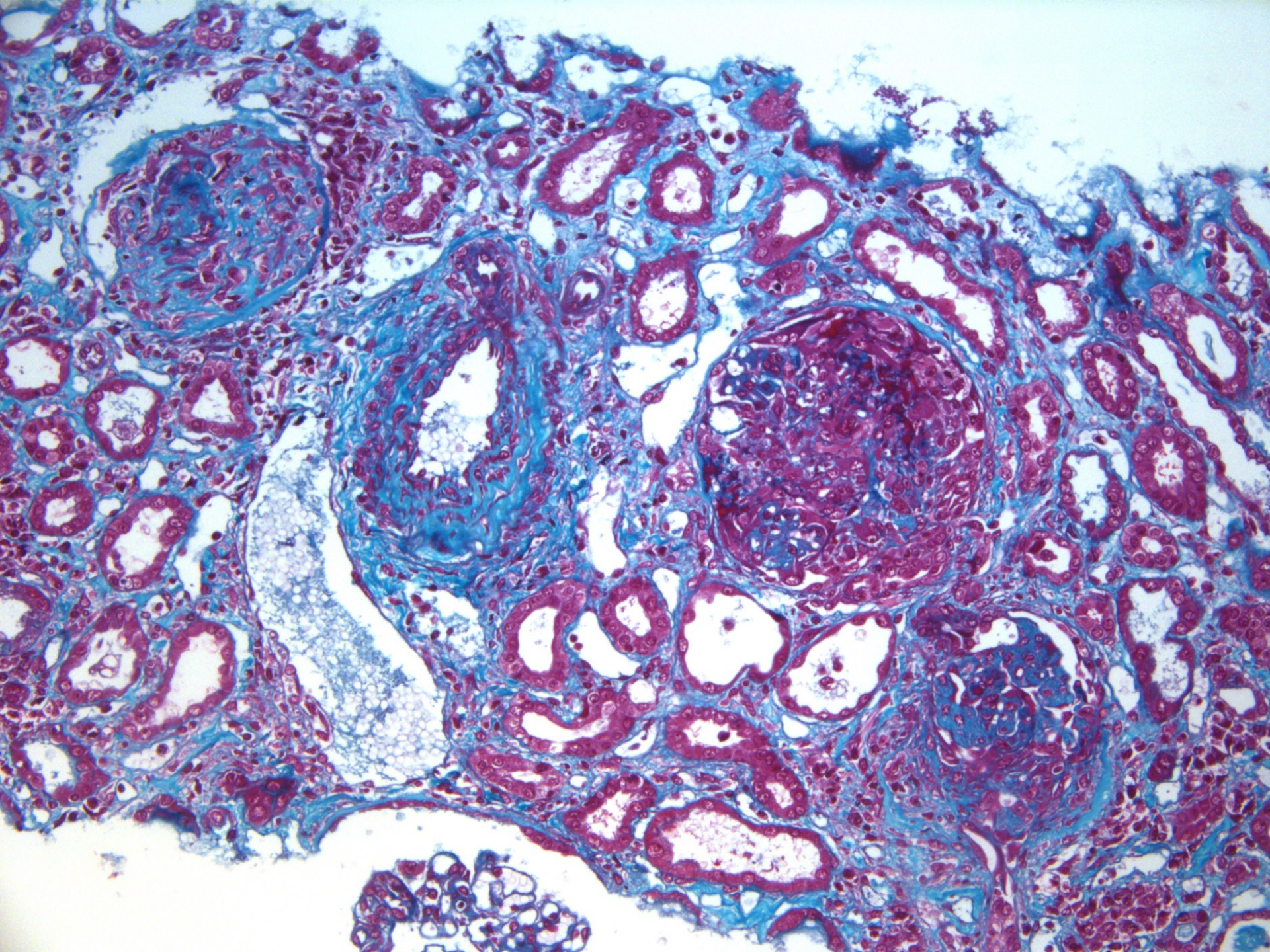
Glomérule normal

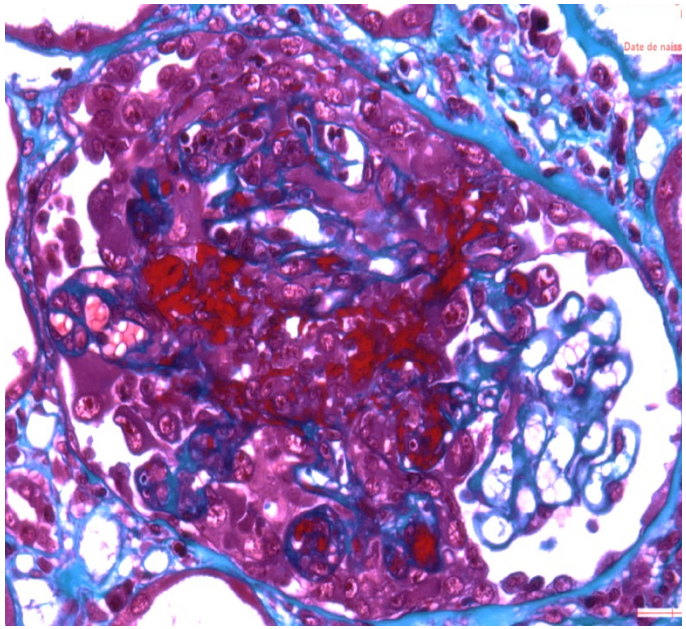


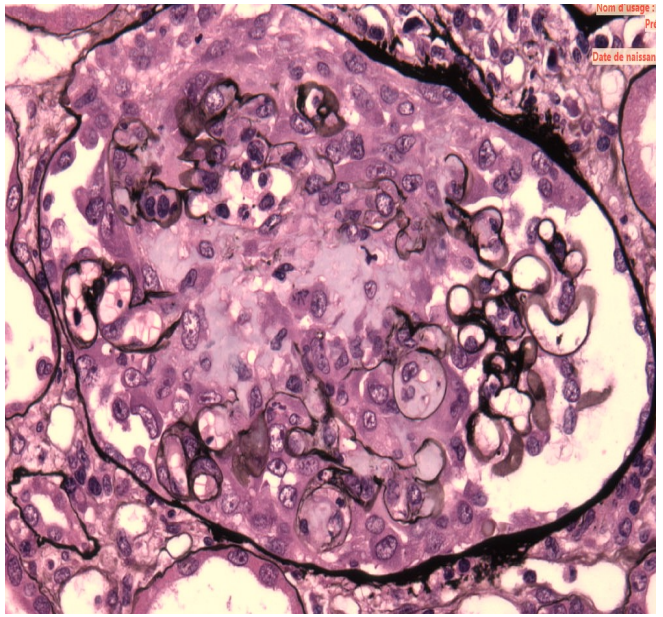
Croissant fibreux ancien

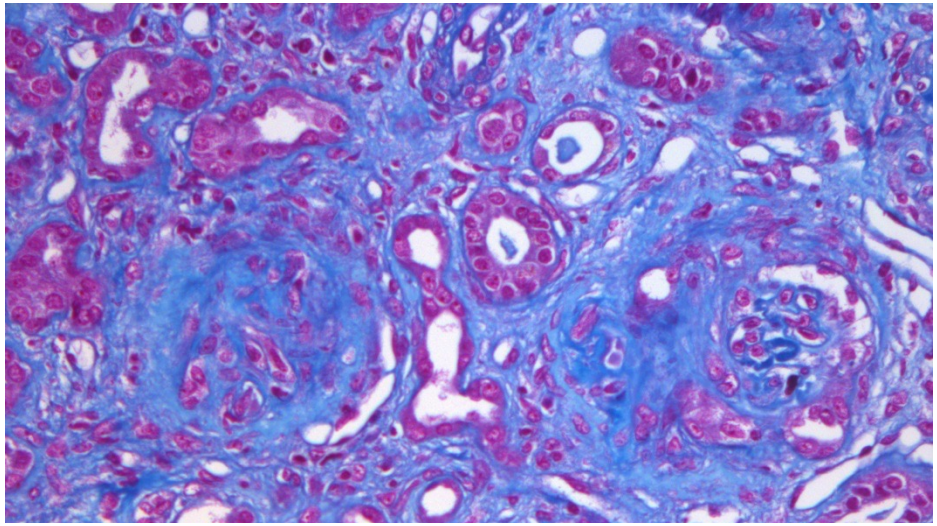


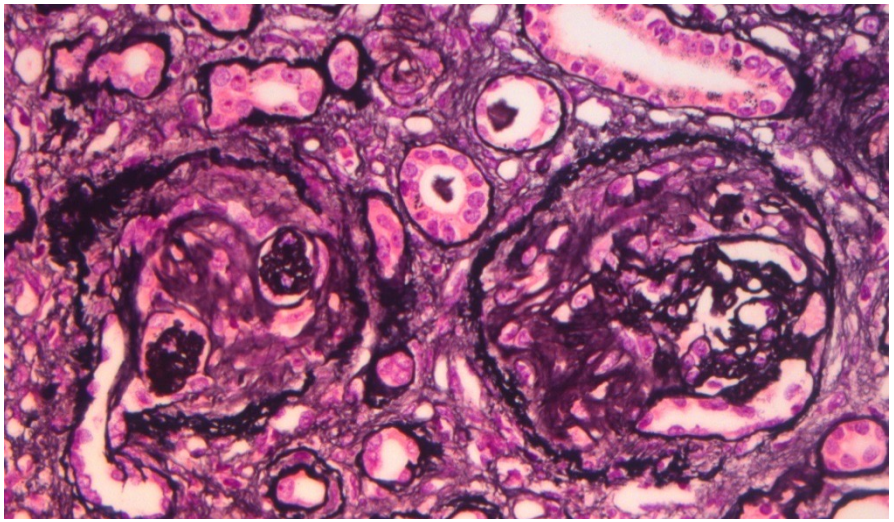
Boud'hors Autoimmunity Reviews 2022



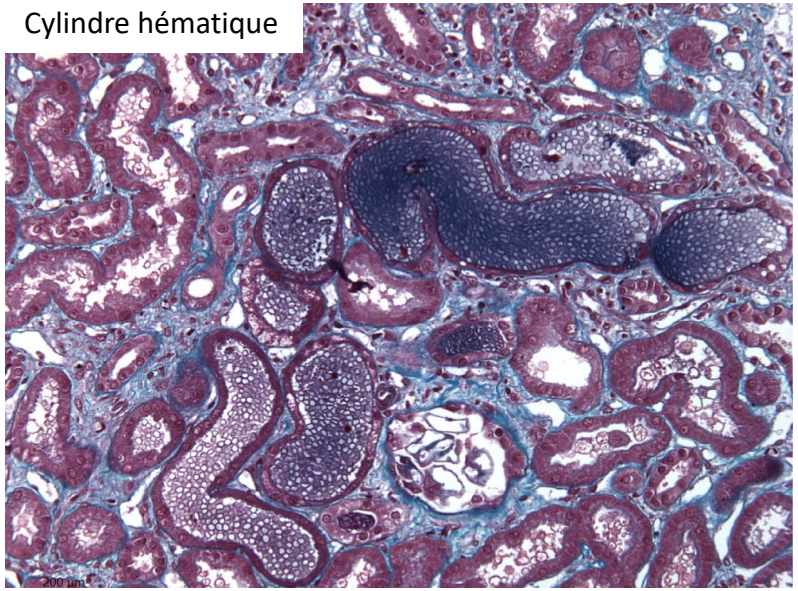




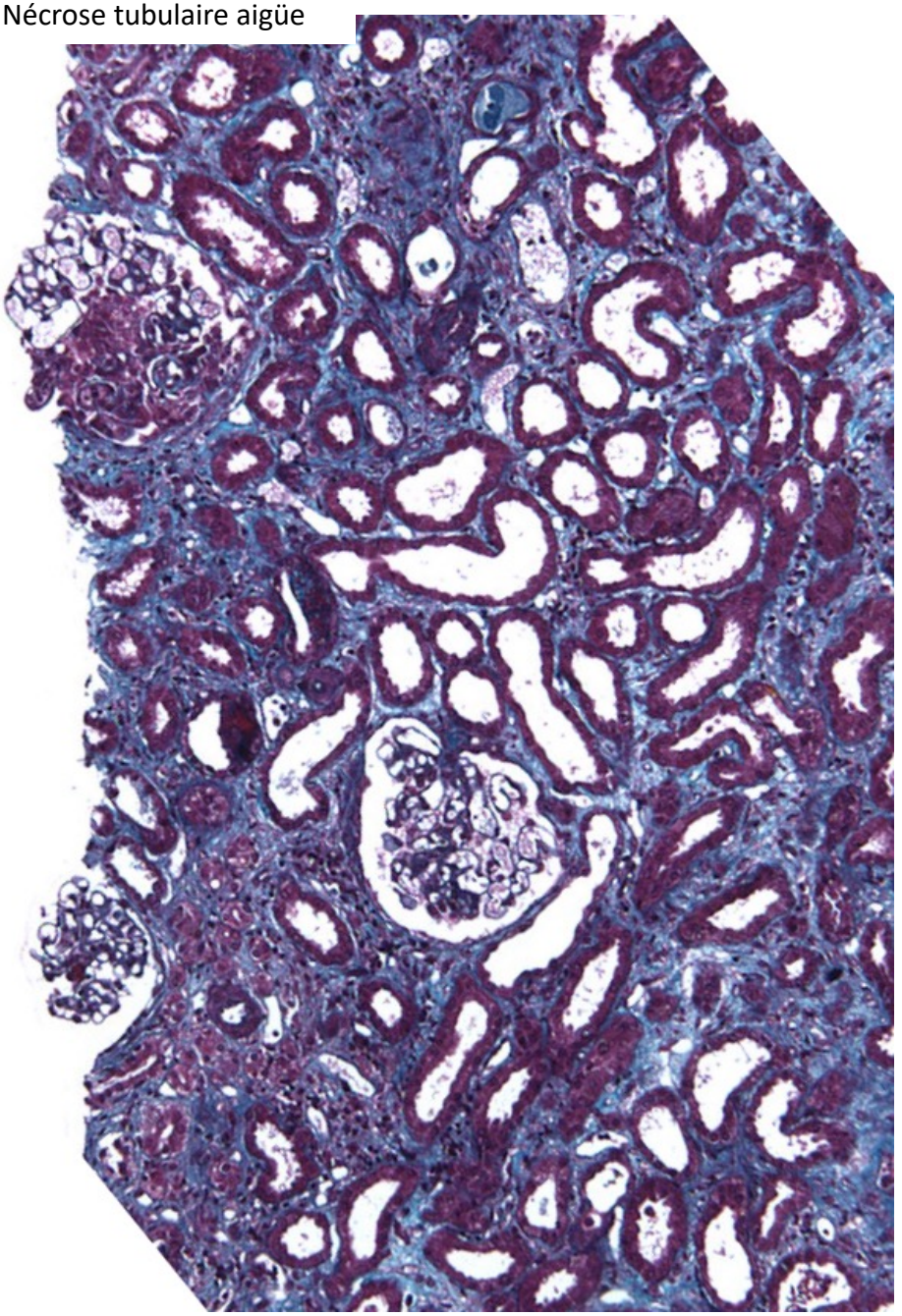




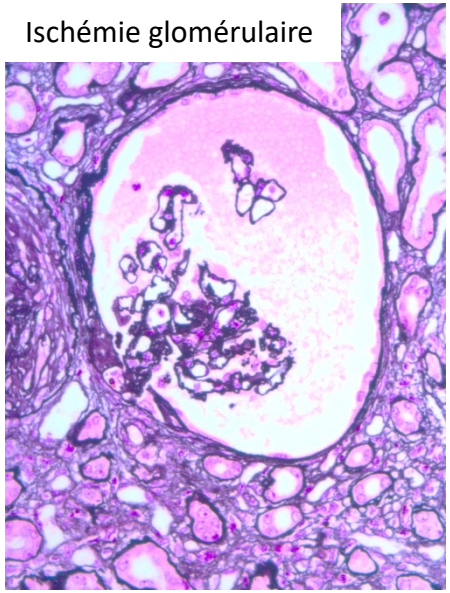
Cylindre hématique

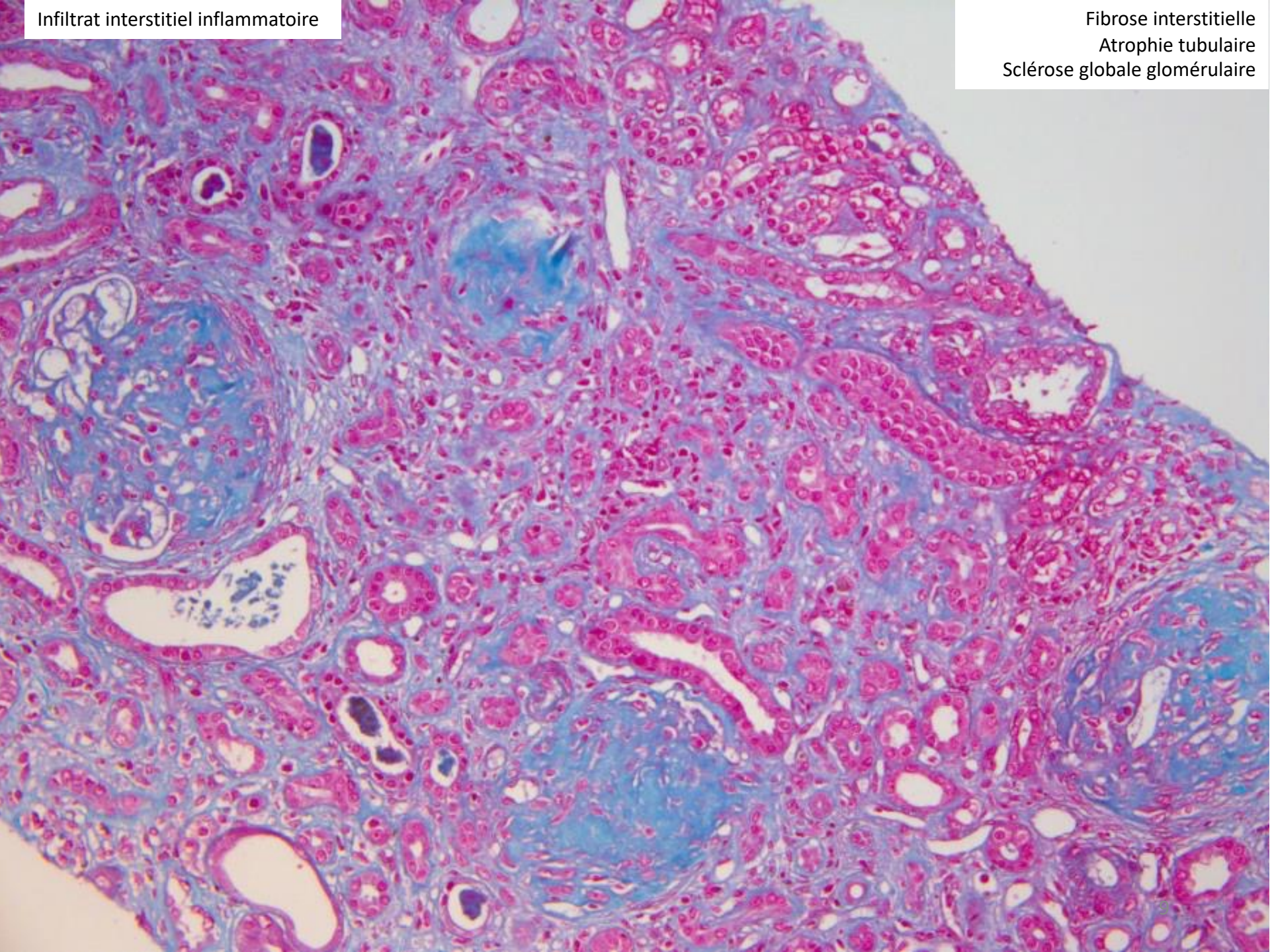


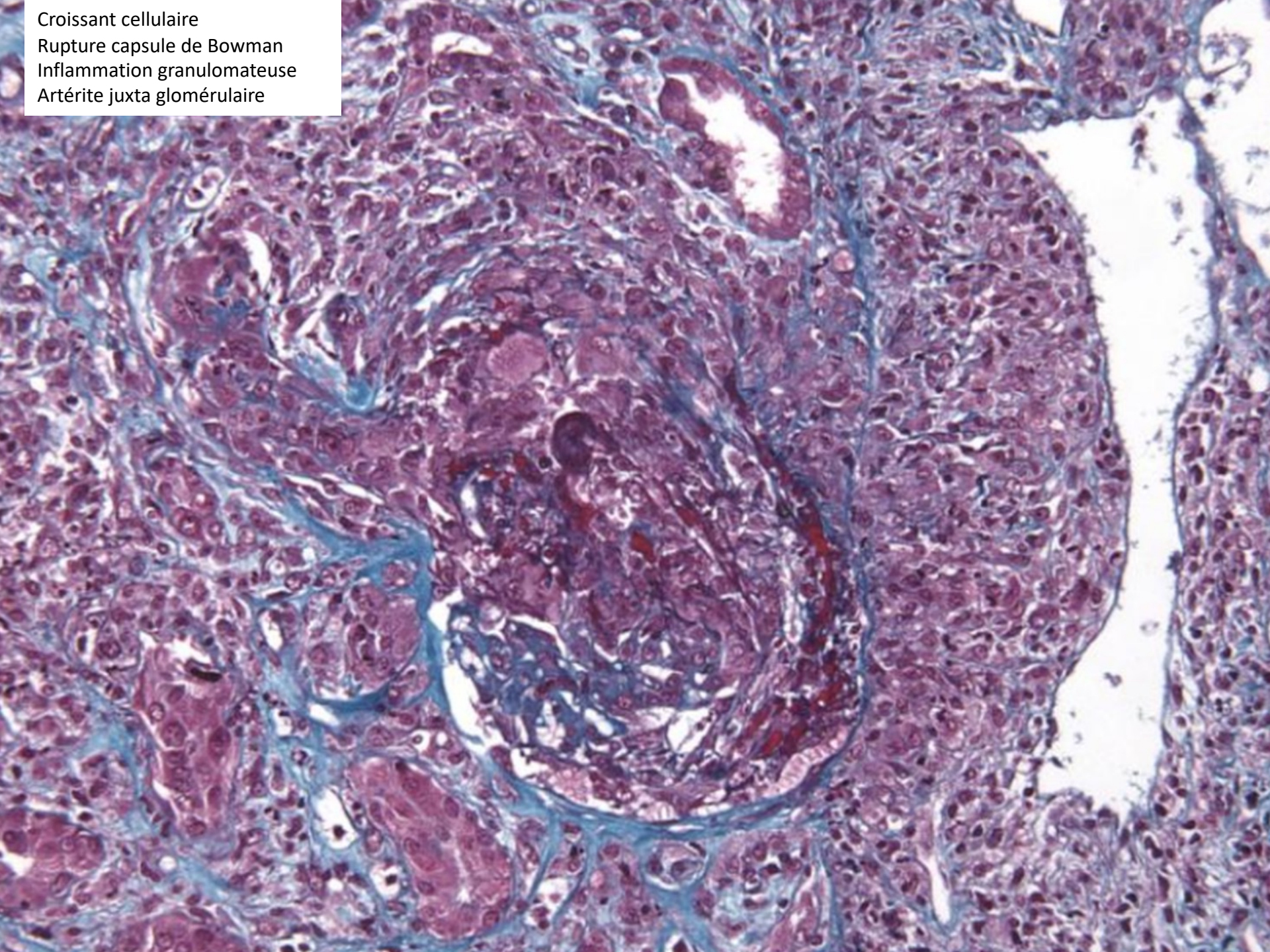
Nécrose tubulaire aigüe

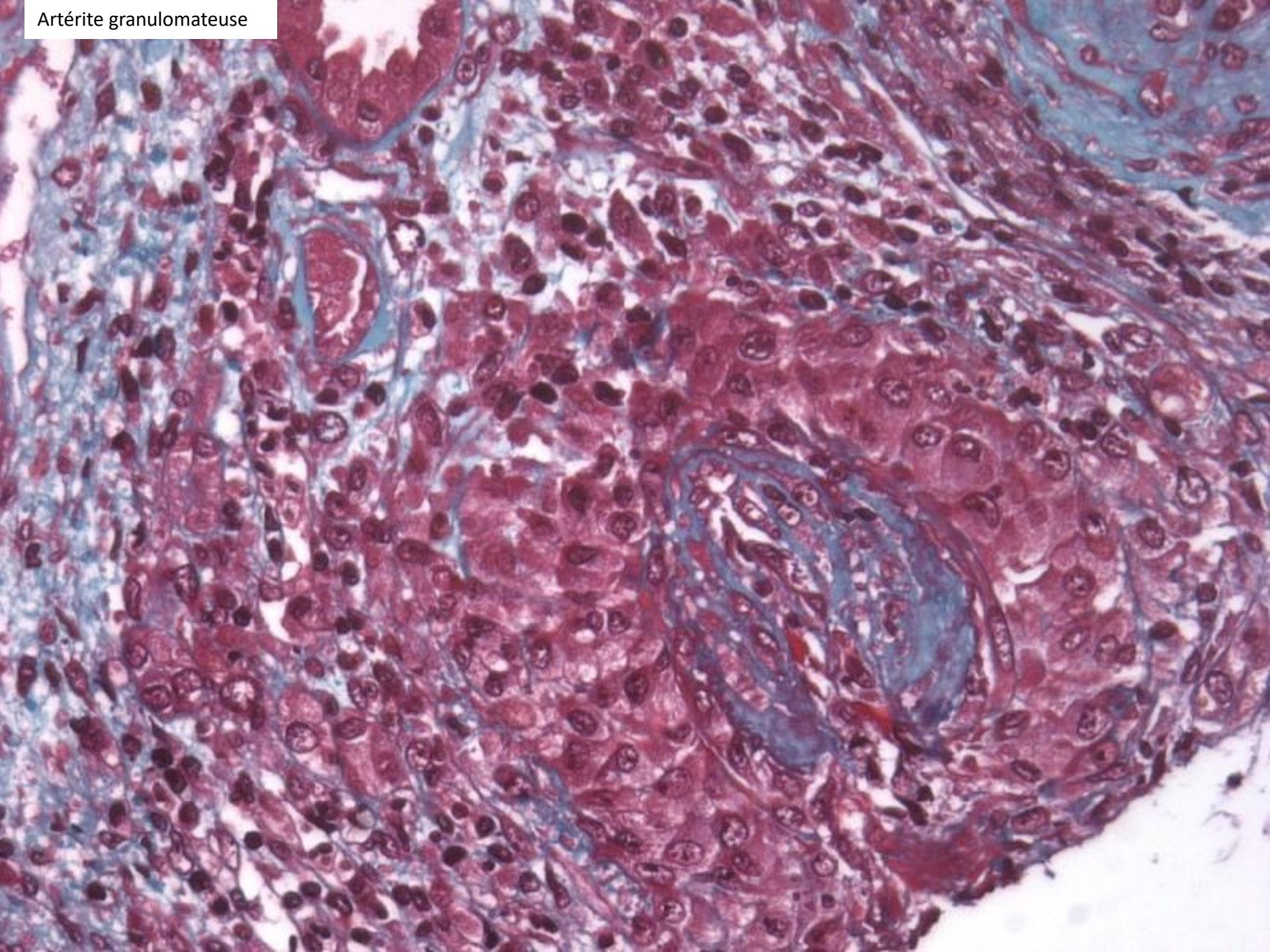


Ischémie glomérulaire




Infiltrat interstitiel inflammatoire
Fibrose interstitielle
Atrophie tubulaire
Sclérose globale glomérulaire


Croissant cellulaire
Rupture capsule de Bowman
Inflammation granulomateuse
Artérite juxta glomérulaire

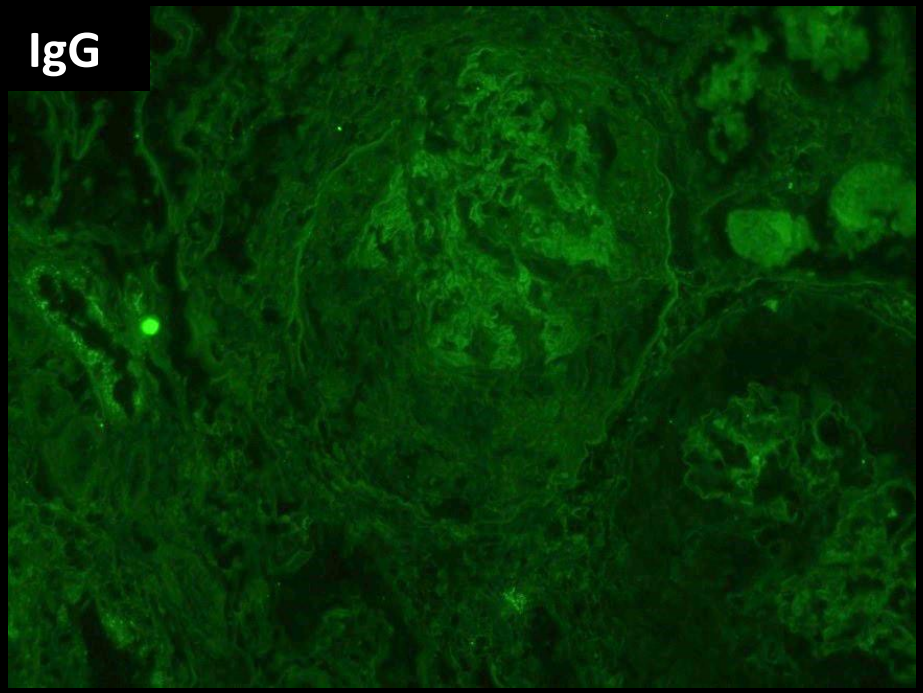

Artérite granulomateuse

AAV : description histopathologique

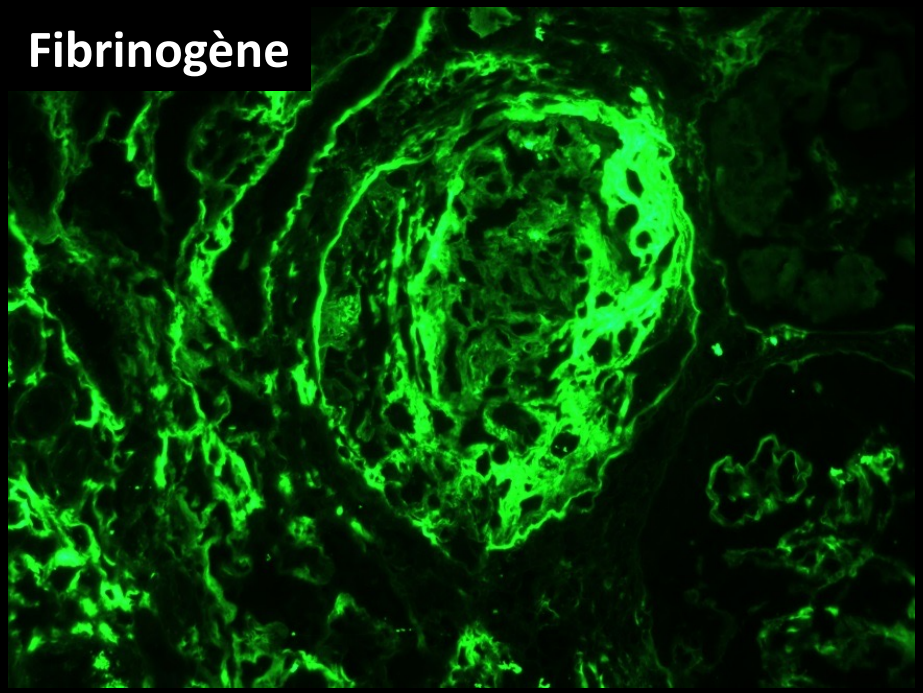
« Pauci immune » : < fixation Ig 2+

Fixation de fibrinogène en regard des nécroses capillaires

IgG

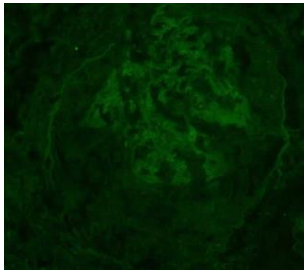
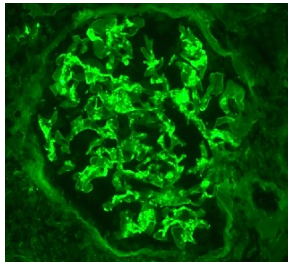
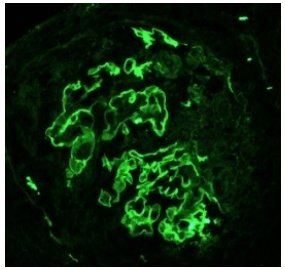


Fibrinogène



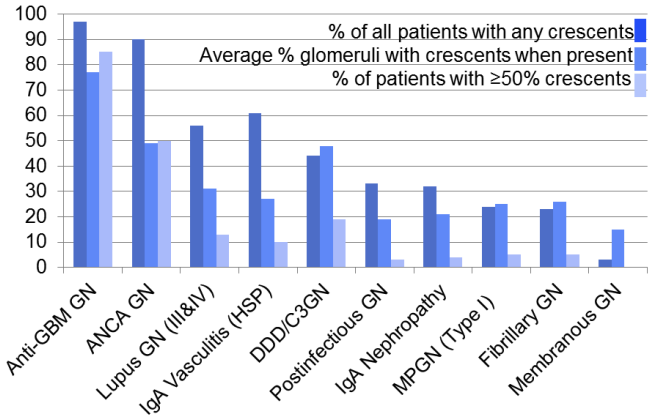
Diagnostics différentiels :

- GNEC pauci immune induite par médicament (levamisole, hydrazaline, propylthiouracil, minocycline…)
- Autres GNEC : intérêt de IF

	Pauci-immune crescentic glomerulonephritis[a]	Immune-complex crescentic glomerulonephritis[b]	Anti-GBM crescentic glomerulonephritis[c]	Other crescentic glomerular disease[d]
All (N = 632)	60% 377/632	24% 154/632	15% 92/632	1% 9/632
Age 1 to 20 years (N = 73)	42% 31/73	45% 33/73	12% 9/73	0% 0
Age 21 to 60 years (N = 303)	48% 145/303	35% 106/303	15% 44/303	3% 8/303
Age 61 to 100 years (N = 256)	79% 201/256	6% 15/256	15% 39/256	0% 1/256

% de croissants/biopsie



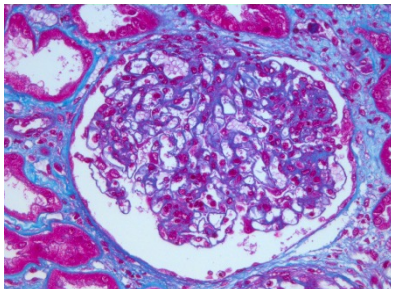
Jennette Kidney Int 2003

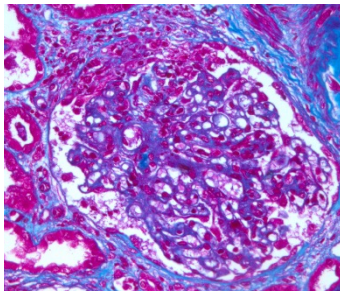
Diagnostic différentiel : GNEC à complexes immuns

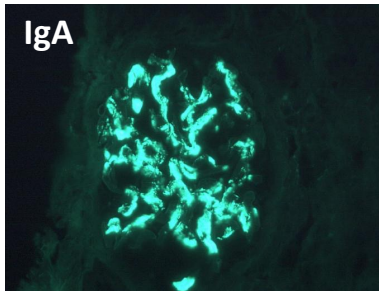
Vascularite à IgA

prolifération mésangiale, endocapillaire

croissants : 40%







<u>IF : dépôts mésangiaux IgA</u>

Néphropathie à IgA + AAV

Rare

ANCA + chez <2% patients IgAN

Pronostic discuté

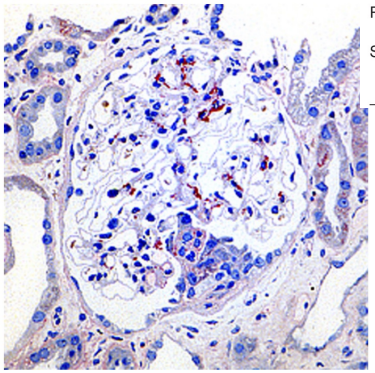
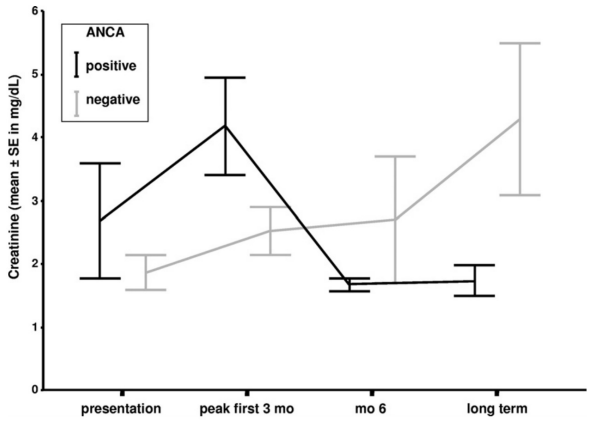


Table 2. Clinical Characteristics of Patients With Crescentic Immunoglobulin A Nephropathy According to the Presence or Absence of ANCAs

	ANCA Positive	ANCA Negative
No. of patients	8	26
Age (y)	56.0 ± 6.3	34.5 ± 12.7
Initial SCr (mg/dL)	2.7 ± 2.6	1.9 ± 1.4
Initial eGFR (mL/min/ 1.73 m^2)	49.3 ± 31.7	57.8 ± 28.9
Peak SCr (mg/dL)	4.2 ± 2.2	2.5 ± 1.9
Lowest eGFR (mL/min/ 1.73 m^2)	19.3 ± 10.2	45.9 ± 30.1
Proteinuria (g/24 h)	3.9 ± 2.4	3.2 ± 2.8
Hemoglobin (g/dL)	10.5 ± 2.0	12.7 ± 1.5
Mean arterial blood pressure (mm Hg)	105.5 ± 8.1	104.2 ± 16.7
Macrohematuria (%)	37.5	23.1
Systemic symptoms (%)	87.5	38.5
Rapidly deteriorating kidney function (%)	100	36
Stable or gradually decreasing kidney function (%)	—	64



Bantis AJKD 2010

Diagnostic différentiel : GNEC à complexes immuns

7,5% patients dépôts > 2+

Dépôts fréquents de complément

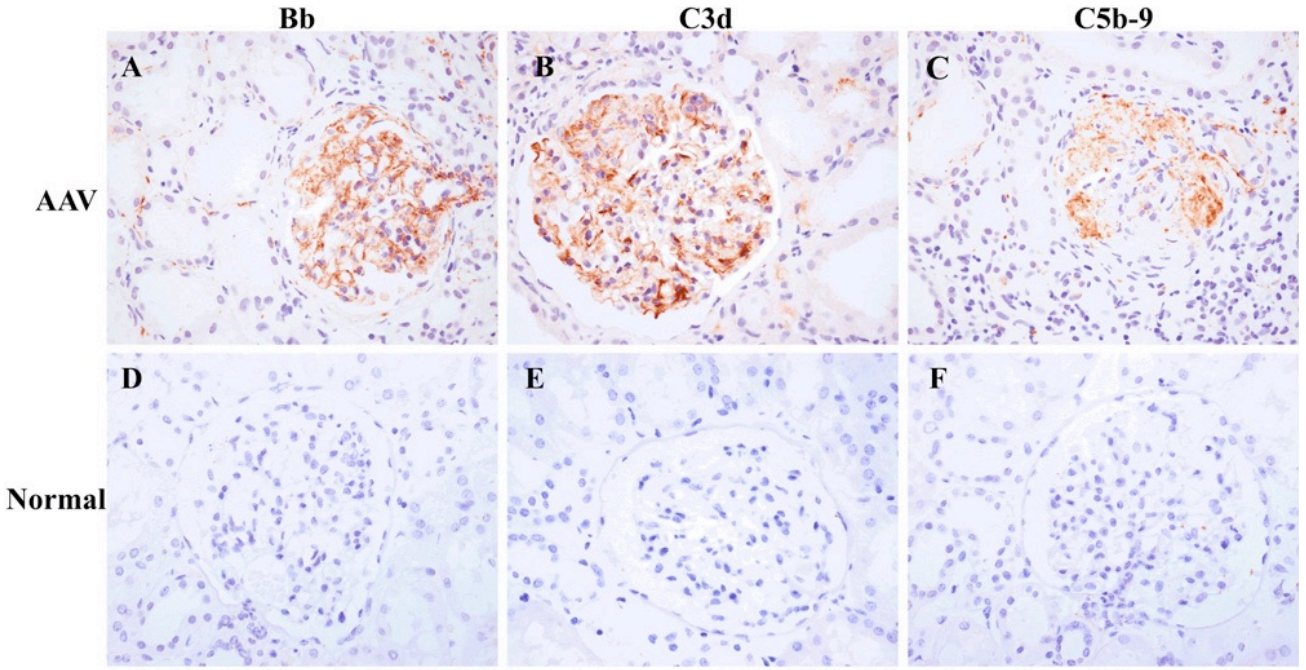
n= 187 patients

C3c 40%

C3d 58% associé au croissant et protéinurie

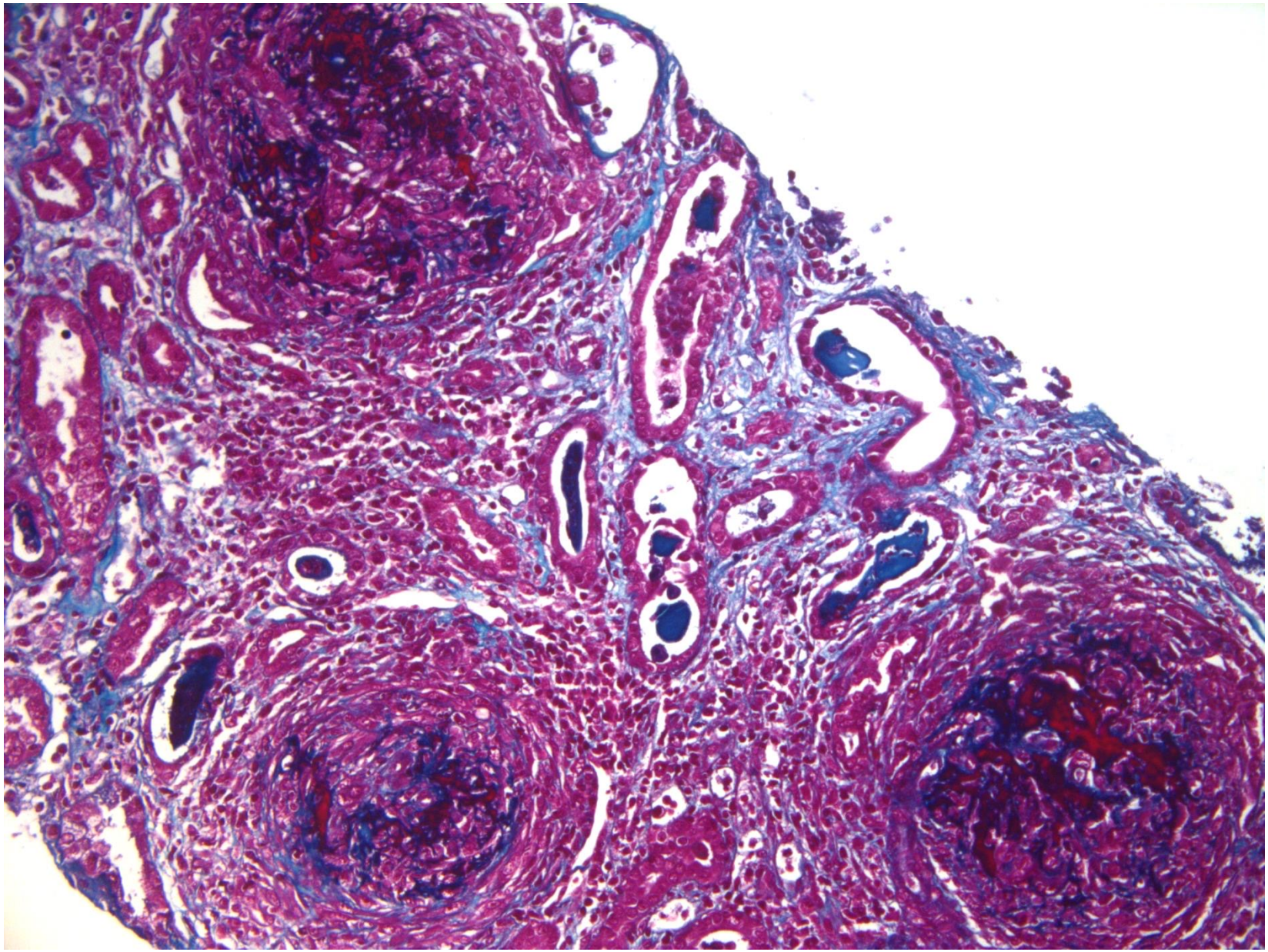
C4d 71% des PBR

Hilhorst NdT 2015

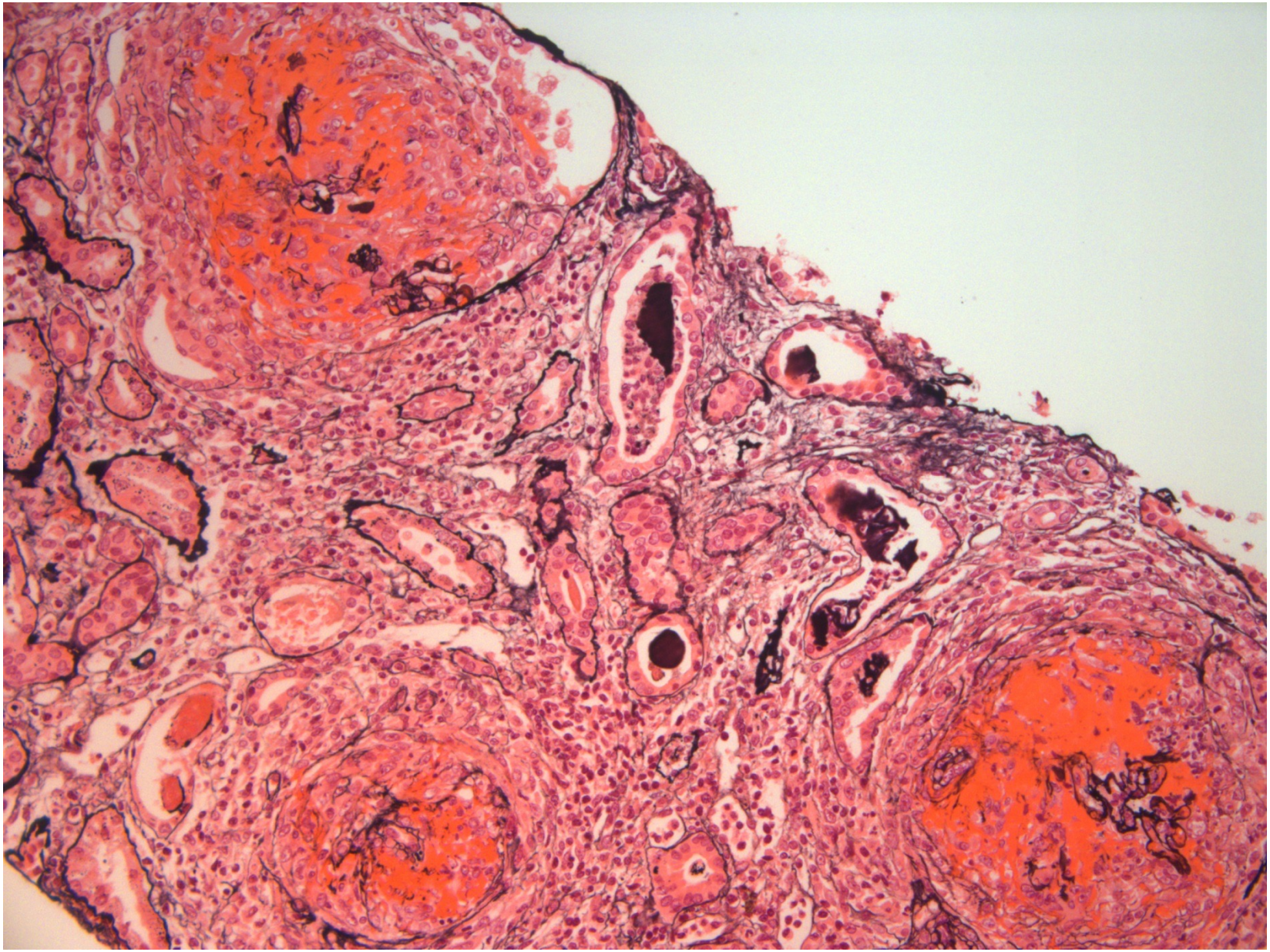


Gou CJASN 2013

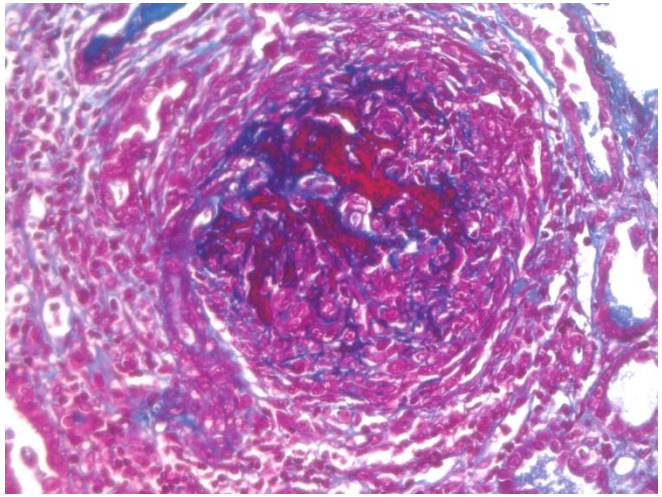
Diagnostic différentiel : GNEC anti MBG

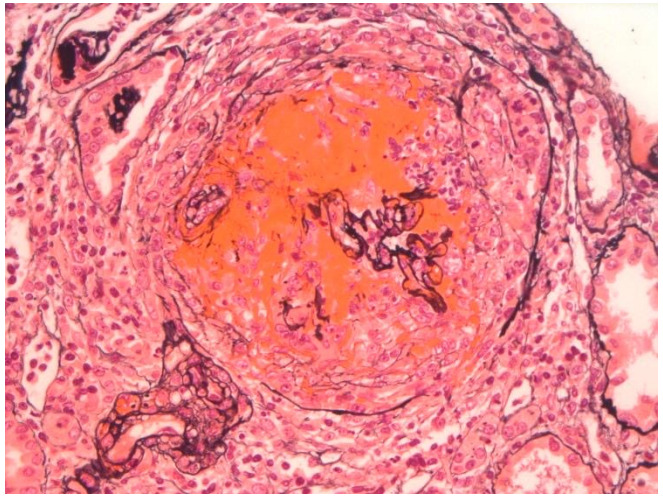


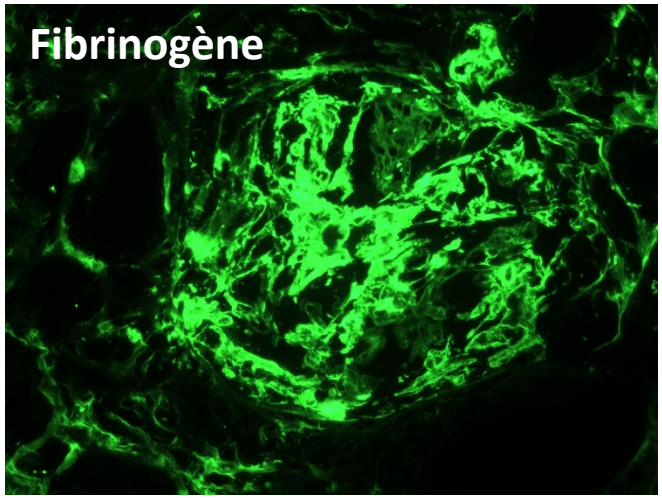
Diagnostic différentiel : GNEC anti MBG

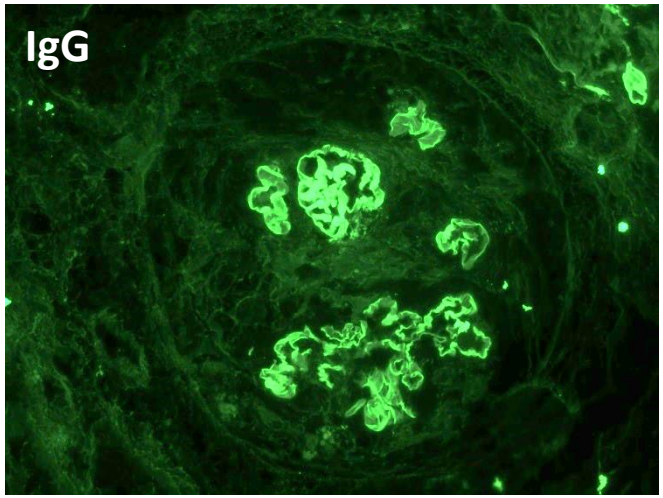


Diagnostic différentiel : GNEC anti MBG









IF fixation intense linéaire le long des MBG

Diagnostic différentiel : anti MBG « atypique »

Présentation clinique moins brutale que anti MBG classique

Auto Ac <u>non détectables</u>

GNEC moins diffuse

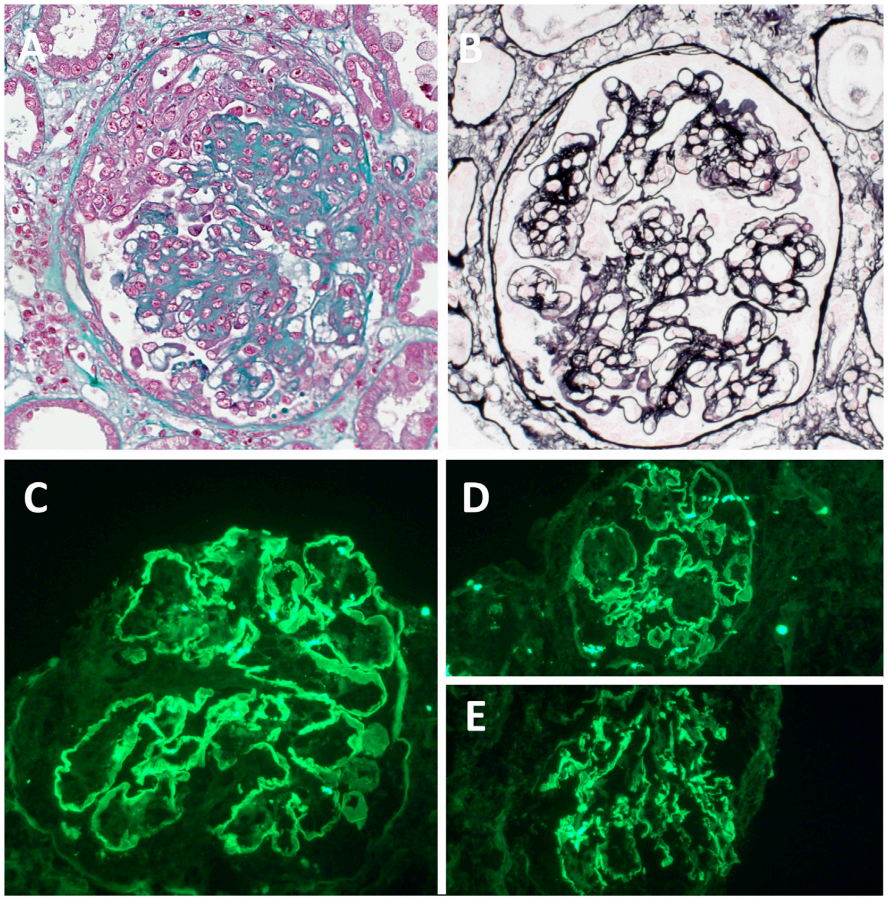
Hypercellularité mésangiale ou endocapillaire

Sclérose glomérulaire 80%

MAT associée 40%

IF : dépôts linéaires IgG

Traces de C3



Chauveau AJKD 2024

Diagnostic différentiel : double positifs anti MBG et ANCA

Anti GBM chez 6% patients AAV

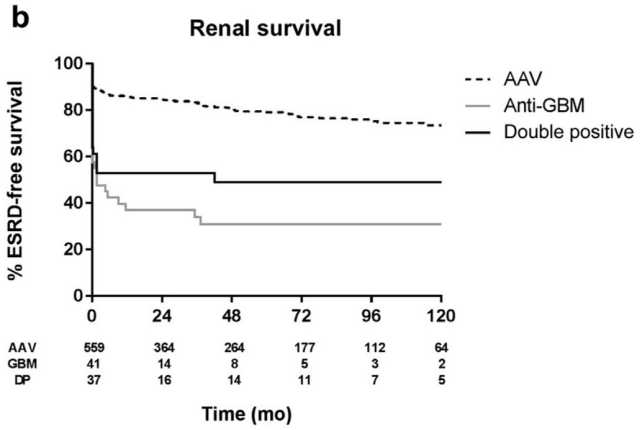
MPO ANCA 70%

Atteinte rénale constante

Atteinte pulmonaire 30%

IF : dépôts linéaires IgG

Survie rénale intermédiaire entre anti GBM et AAV

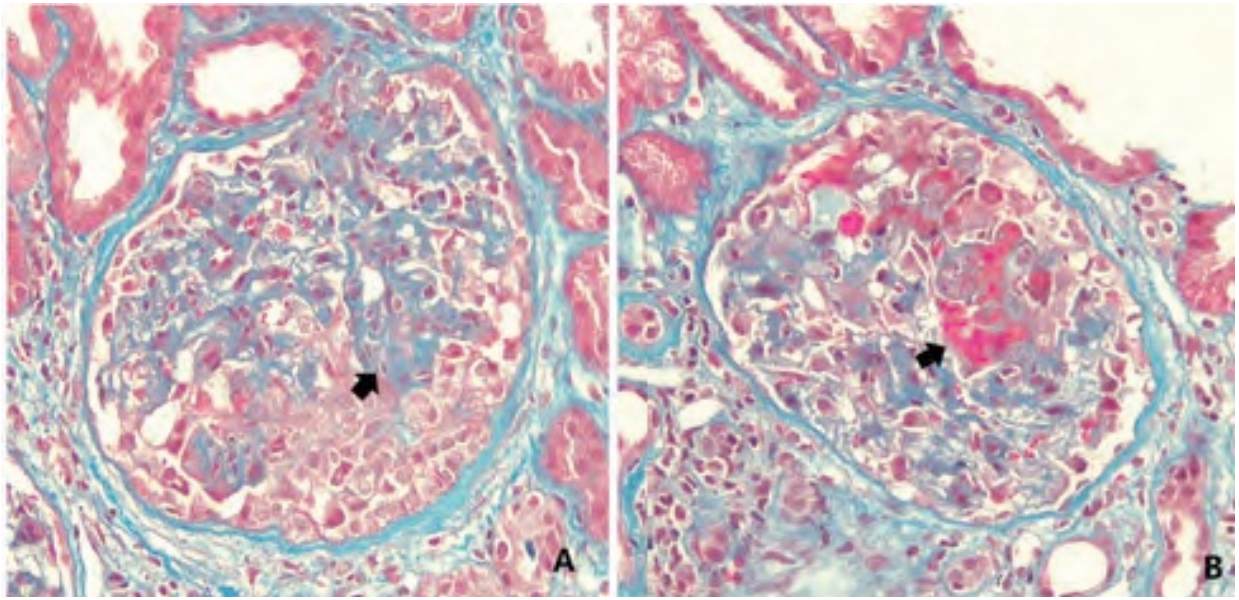


	Anti-GBM	Double positive	*P* value
Underwent biopsy, n (%)	29 (71%)	25 (68%)	0.81
Mean age at biopsy, yr (range)	46 (13–91)	62 (46–76)	**<0.01**
Renal status at biopsy			
• Required RRT	52%	54%	1.00
• eGFR,[a] ml/min (range)	21 (5–90)	16 (8–73)	0.78
• Serum creatinine[a] µmol/l (range)	275 (62–677)	315 (71–606)	0.75
Glomerular findings			
• Crescentic glomeruli, %	64% (0–100)	64% (25–100)	0.98
• Sclerotic glomeruli, %	0% (0–80)	15% (0–100)	0.19
• Normal glomeruli, %	5% (0–100)	0% (0–67)	0.56
Tubular atrophy, % (range)	5% (0%–30%)	27% (0%–80%)	**<0.01**
Immunofluorescence pattern			0.69
• Linear IgG	79%	80%	
• Pauci-immune	3%	8%	
• Technically inadequate	17%	12%	

eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; RRT, renal replacement therapy.
Results expressed as median ± range. Comparison between groups by Mann-Whitney test (for continuous data), or by chi-square test (for categorical data).
[a]Censored for patients on RRT.

McAdoo Kidney Int 2017

Diagnostic différentiel : pseudo croissant



HSF collapsing

Croissant cellulaire

Malek AJKD 2021

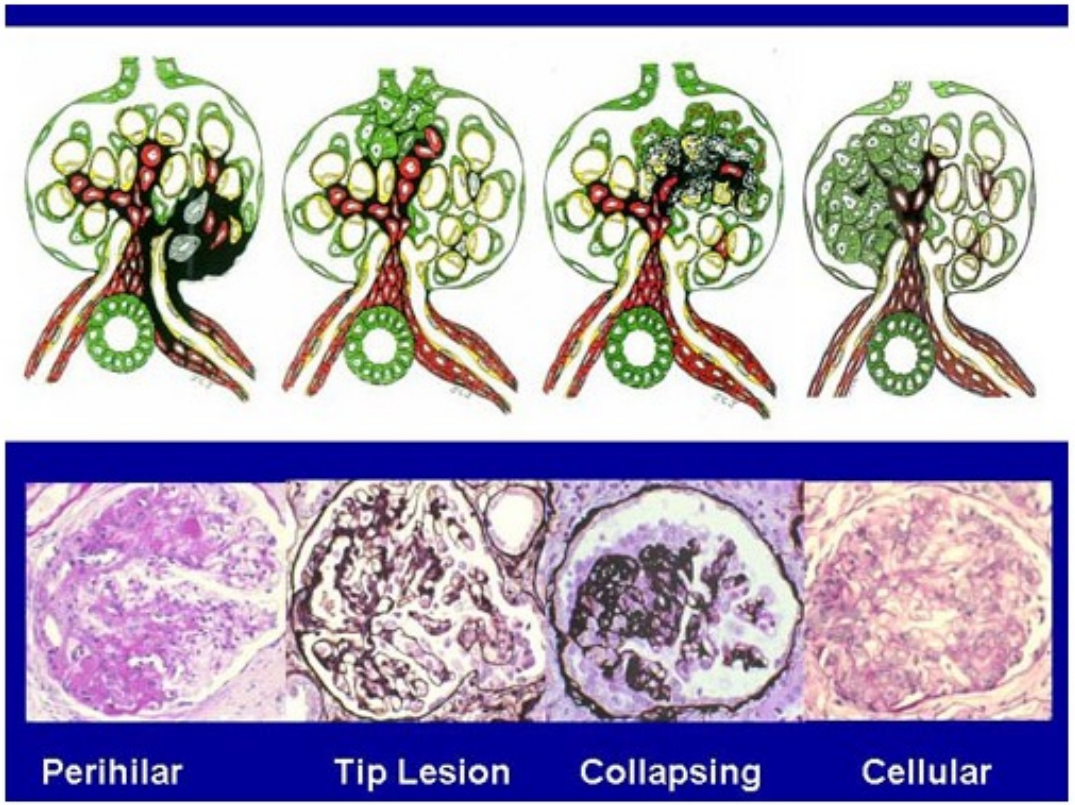
Diagnostic différentiel : pseudo croissant

Clinique : Syndrome néphrotique

Microscopie :
Sclérose segmentaire éosinophile, argyrophile
Hyalinose (dépôts de protéine plasmatique)
Synéchie floculo-capsulaire

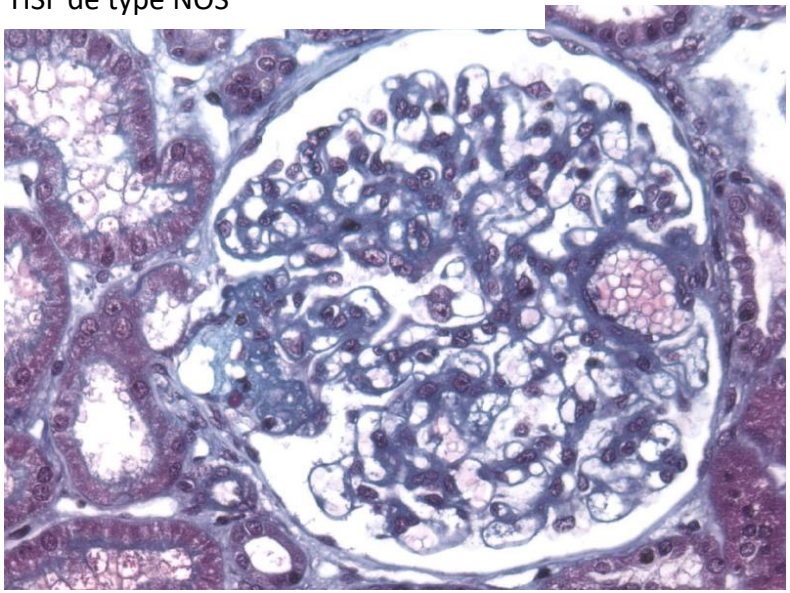
Podocytes hyperplasiques formant une couronne
Halo clair sous-podocytaire
Macrophages spumeux

5 types d'HSF selon Columbia

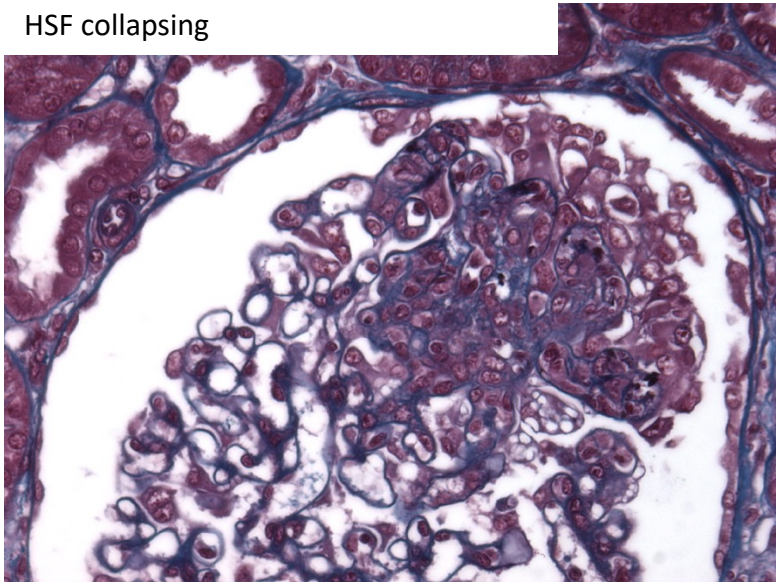


Diagnostic différentiel : pseudo croissant

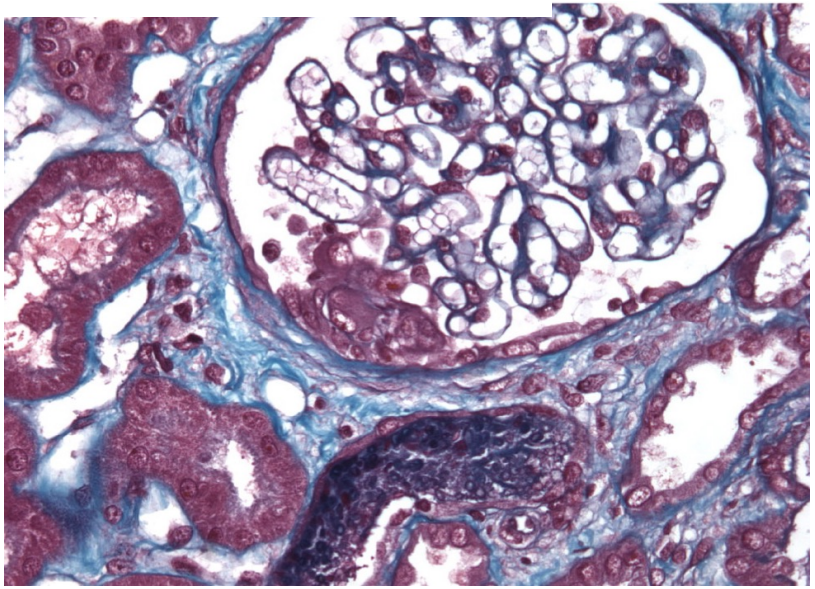
HSF de type NOS



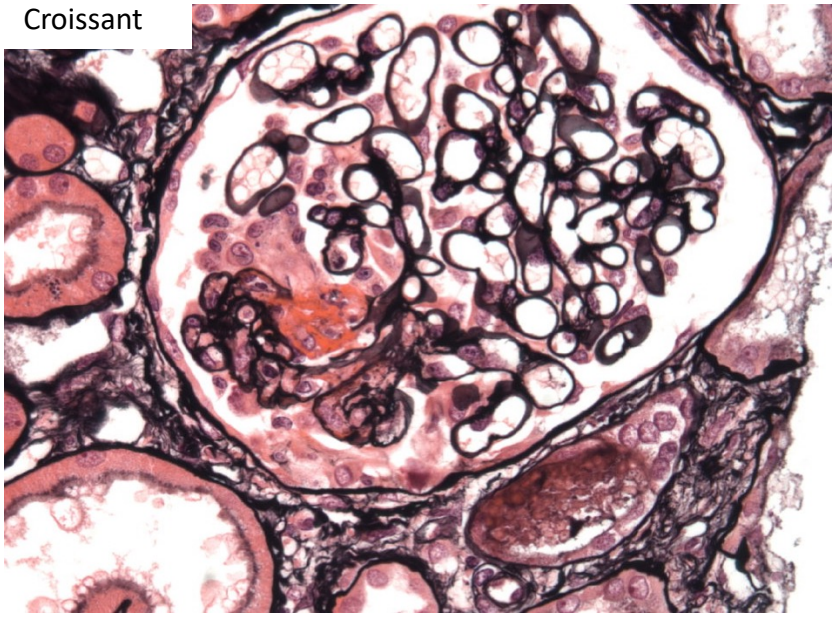
HSF collapsing



Croissant débutant



Croissant



Apport pronostique PBR dans AAV

Facteurs cliniques et biologiques pronostiques de survie rénale :

- âge avancé,
- eGFR au diagnostic initial
- protéinurie, réponse au traitement, rechutes rénales

Facteurs histologiques :

- Nombre (%) de pains à cacheter
- Nombre (%) de glomérule normal
- % de fibrose interstitielle et atrophie tubulaire (FIAT)

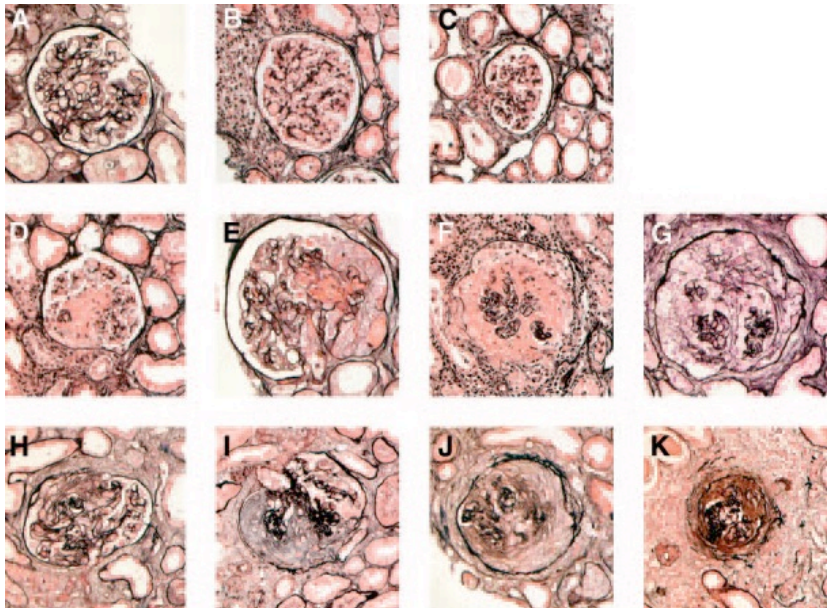
4 classifications histo-pronostiques dans AAV :

- Berden/EUVAS en 2010
- Mayo Clinic chronicity score (MCCS) en 2019 – validée pour AAV en 2022
- Brix/ANCA Renal Risk Score (ARRS) en 2018
- Improved in new ANCA kidney Risk score (AKRiS) en 2023

Apport pronostique PBR dans AAV

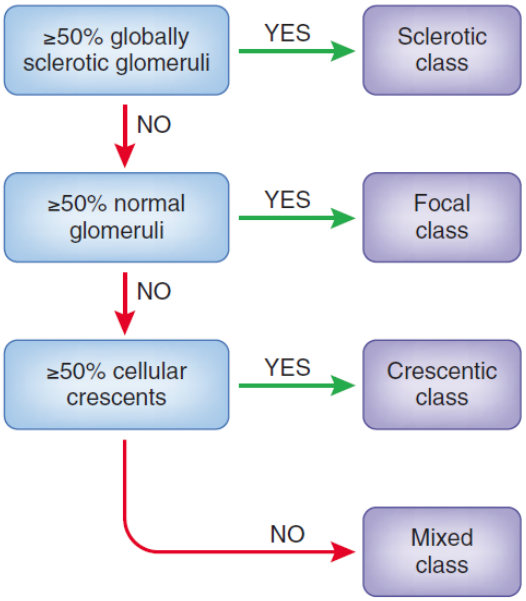
Classification Berden/EUVAS

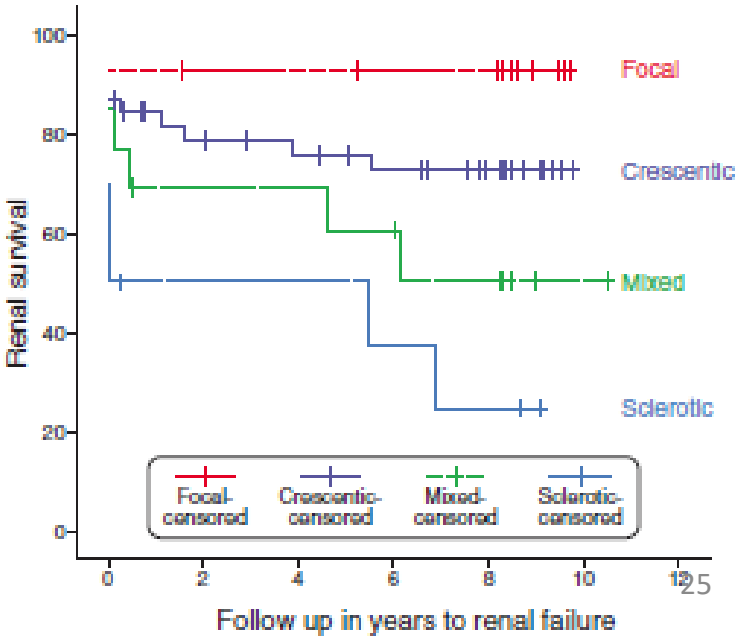
Basée sur glomérules



Berden JASN 2010

k = 0,56
Au moins 10 glomérules analysables
(validée entre 5 et 9 glomérules)





Apport pronostique PBR dans AAV

Classification Sethi Mayo

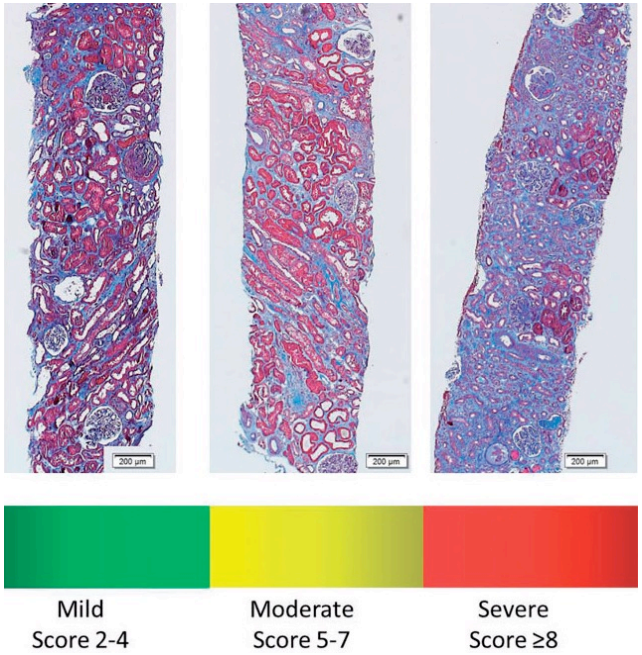
Basée sur glomérules + FIAT + cv

Mayo Clinic chronicity score

1. Global and segmental glomerulosclerosis (0–3)^
2. Tubular atrophy (0–3)^
3. Interstitial fibrosis (0–3)^
4. Arteriosclerosis (0–1)**

0 = < 10%
1 = 10–25%
2 = 26–50%
3 = > 50%
** Intimal thickening ≥ media thickness = 1

Minimal	0–1
Mild	2–4
Moderate	5–7
Severe	≥ 8



Sethi Ndt 2019

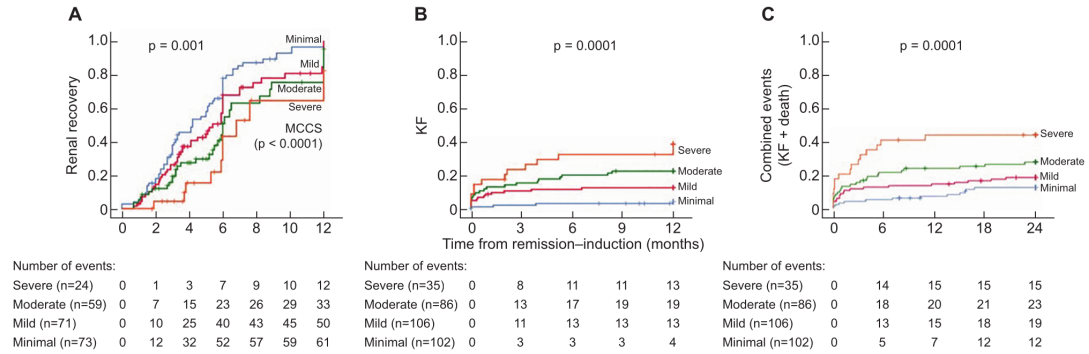


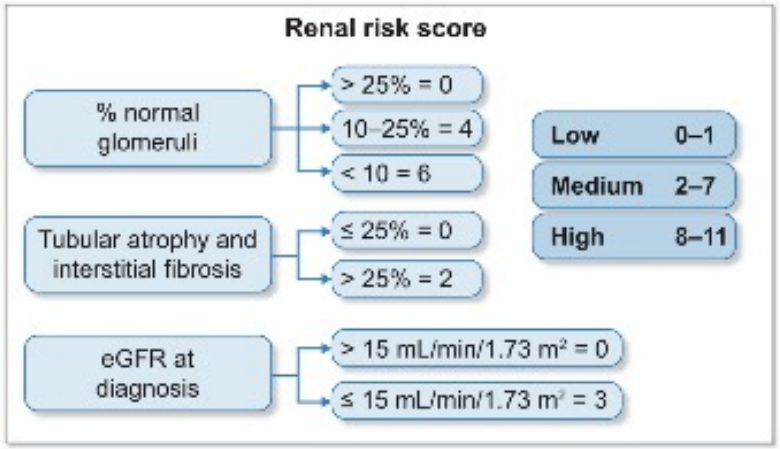
FIGURE 4: Kaplan–Meier plots of renal outcomes. (**A**) Renal recovery (with minimal eGFR ≥30 mL/min/1.73 m^2) and remission for 12 months: 61 versus 50 versus 33 versus 10, mean time to event 4.6 versus 5.9 versus 6.7 versus 7.9 months; P = 0.001. (**B**) KF at 12 months (minimal versus mild versus moderate versus severe): 4 versus 13 versus 19 versus 13 events, mean time to event 11.7 versus 10.7 versus 9.9 versus 8.7 months; P < 0.0001. (**C**) Combined events of KF and/or death over 24 months (minimal versus mild versus moderate versus severe): 12 versus 19 versus 23 versus 15 events, mean time to event 22.1 versus 20.6 versus 18.7 versus 14.8 months; P < 0.0001.

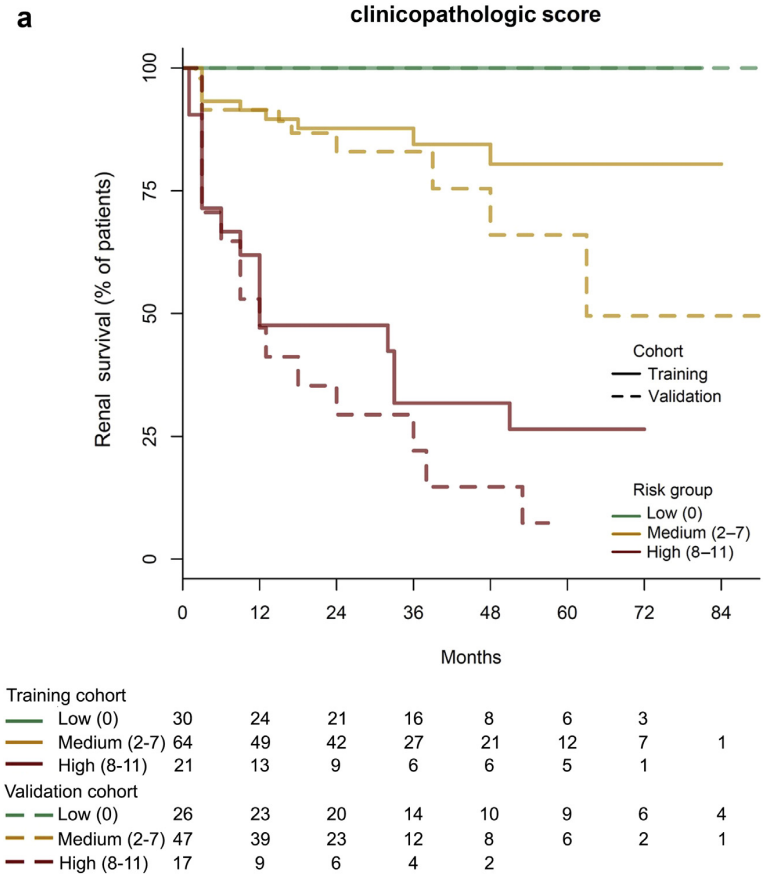
Casal Moura Ndt 2022

Apport pronostique PBR dans AAV

ANCA Renal Risk Score ARRS

Score composite : histo + clinique





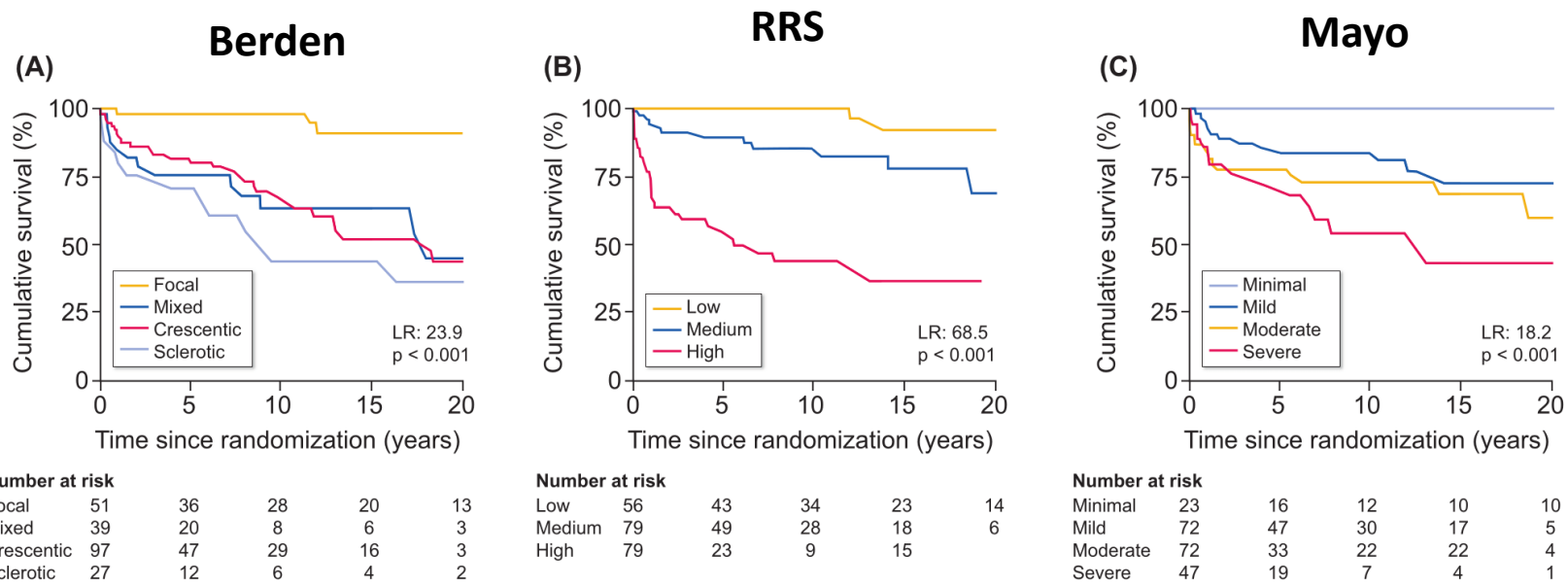
b

Renal survival 36 months

Risk group	Training (95% CI)	Validation (95% CI)
Low	100% (100)	100% (100)
Medium	84% (75–95)	83% (72–96)
High	32% (17–60)	22% (9–56)

Brix KI 2018

Apport pronostique PBR dans AAV



Sanchez-Alamo Ndt 2024

Berden :
Classes croissants et mixtes

RRS :
Validation dans méta analyse,
Très bonne sensibilité sauf pour classe haut risque

Apport pronostique PBR dans AAV

Improved in new **ANCA kidney Risk score** (AKRiS)

Créatininémie remplace eGFR

Nouvelle pondération pour FIAT

4 groupes

The Improved Kidney Risk Score in ANCA-Associated Vasculitis for Clinical Practice and Trials

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

Retrospective longitudinal international cohort study of patients from 11 referral centres and registries.

Of 1591 newly diagnosed ANCA GN patients, analysis of 959 patients in development, 480 in validation study.

January 1987 - February 2022

Multivariable Cox analysis of histopathological + clinical parameters to predict ESKD.

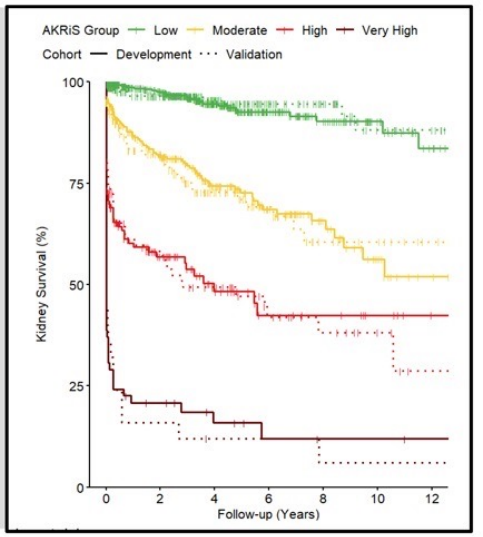
Risk Groups	ESKD at 3yrs
Low	4%
Moderate	11%
High	46%
Very High	81%

RESULTS

ANCA Kidney Risk Score (AKRiS)	Points
Creatinine (µmol/l)	
K0: < 250	0
K1: 250 – 450	4
K2: > 450	11
Normal Glomeruli (%)	
N0: > 25	0
N1: 10 – 25	4
N2: < 10	7
IFTA (%)	
T0: none and mild, < 25%	0
T1: ≥ mild - moderate, ≥ 25%	3

Group	Points
Low	0 – 4
Moderate	5 – 11
High	12 – 18
Very High	21

C(ARRS) = 0.800 (CI 0.768 – 0.832)
C(AKRiS) = 0.831 (CI 0.801 – 0.861)



Conclusion – The ANCA Renal Risk Score (ARRS) provided a strong discriminative ability and the here presented update, the ANCA Kidney Risk Score (AKRiS), improves the existing paradigm. The revised and improved score optimizes clinicopathologic prognostication for clinical practice and trials.

doi:10.1681/ASN.0000000000000274

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Bate JASN 2024

Apport pronostique PBR dans AAV

Comparaison des 4 scores histo AAV

101 patients

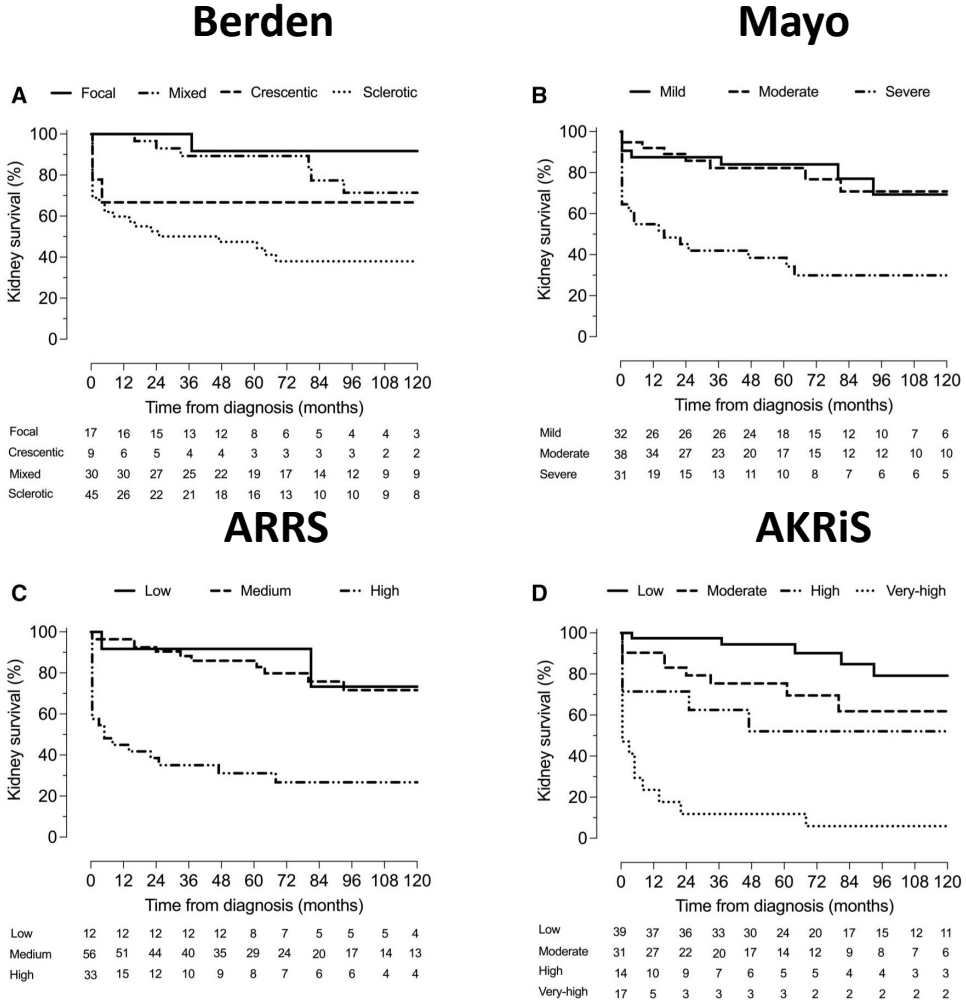


Table 3. Single model and post-treatment parameter performance for prediction of kidney failure

Model/parameter	Harrell's C statistic	95% CI
EUVAS/Berden histologic classification	0.702	0.620–0.784
Mayo Clinic Chronicity Score	0.606	0.473–0.738
Percentage of ANCA chronicity score (PACS)	0.801	0.736–0.867
ANCA Renal Risk score (ARRS)	0.782	0.706–0.858
Improved ANCA kidney risk score (AKRiS)	0.817	0.749–0.885
6-Month post-treatment parameters[a]		
Estimated GFR	0.836	0.746–0.926
Proteinuria	0.757	0.654–0.861
Relapses	0.708	0.588–0.827

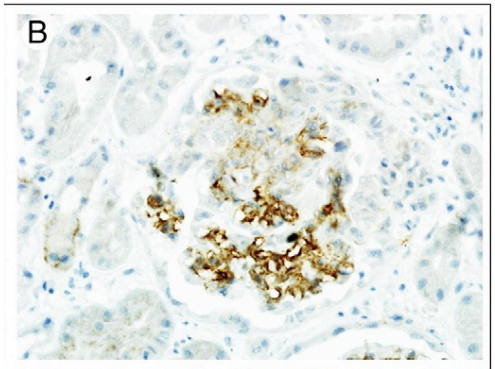
[a] 6-Month post-treatment parameters were evaluated in patients with functional kidney by 6 months.
EUVAS: European Vasculitis Study Group; GFR: glomerular filtration rate.

Sandino-Bermudez Rheumatology 2024

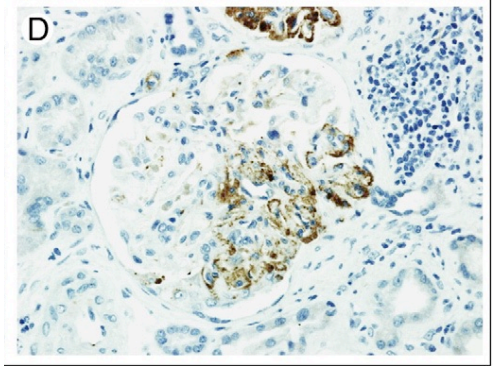
Apport pronostique PBR dans AAV

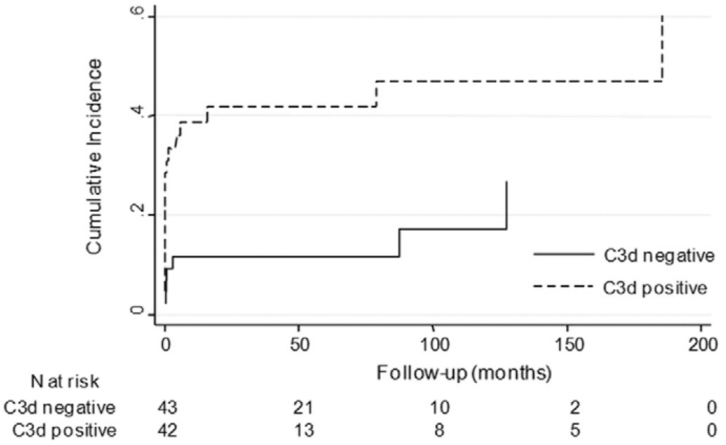
Dépôts de fractions du complément

C3d



C4d





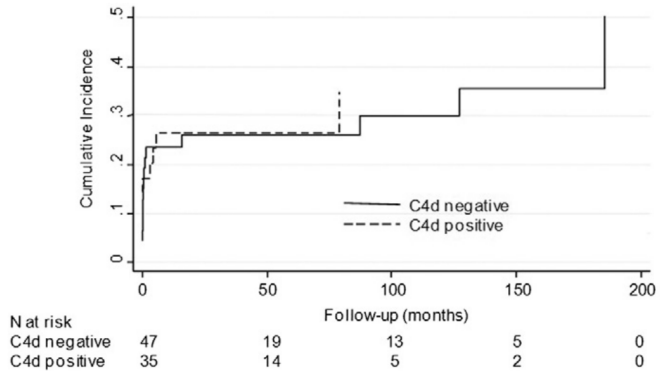


Table 4 Clinical and histologic characteristics associated with the development of ESRD in 85 patients with PCGN

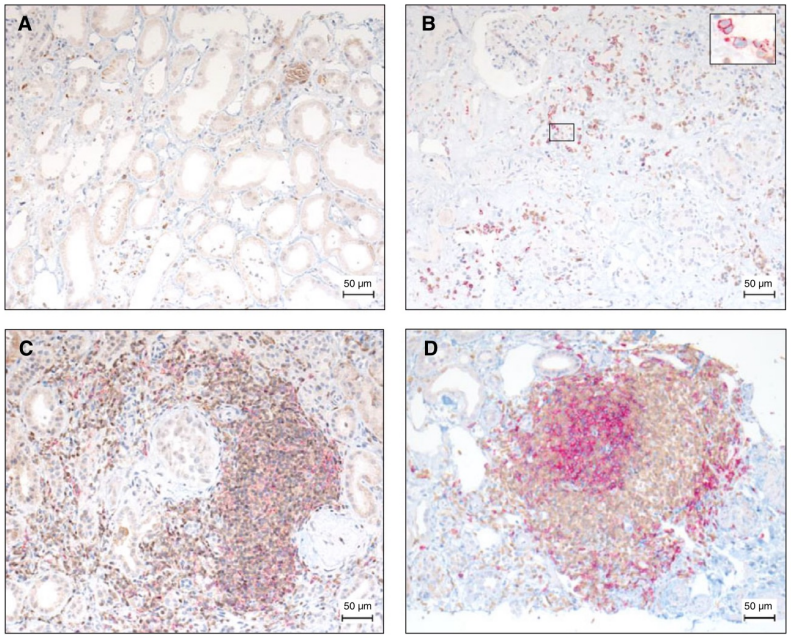
Variable	Developed ESRD (n = 26)	Did not develop ESRD (n = 59)	*P*
Median eGFR at the onset (mL/min) (IQR)	7.2 (4.4-11.5)	21.4 (11.9-42.7)	<.001
% Sclerotic glomeruli (IQR)	22 (6.7-44.2)	11 (0-26)	.03
% Normal glomeruli (IQR)	11 (0-29)	25 (10-40)	.01
Interstitial fibrosis, n (%)	11 (42.3%)	11 (18.6%)	.02
C3d-positive staining, n (%)	19 (73%)	23 (38.9%)	.004

NOTE. *P* value for categorical variables based on a χ^2 test of independence; *P* value for continuous variables based on a 2-sample *t* test for a difference, assuming equal variances.

Villacorta Human Pathology 2016

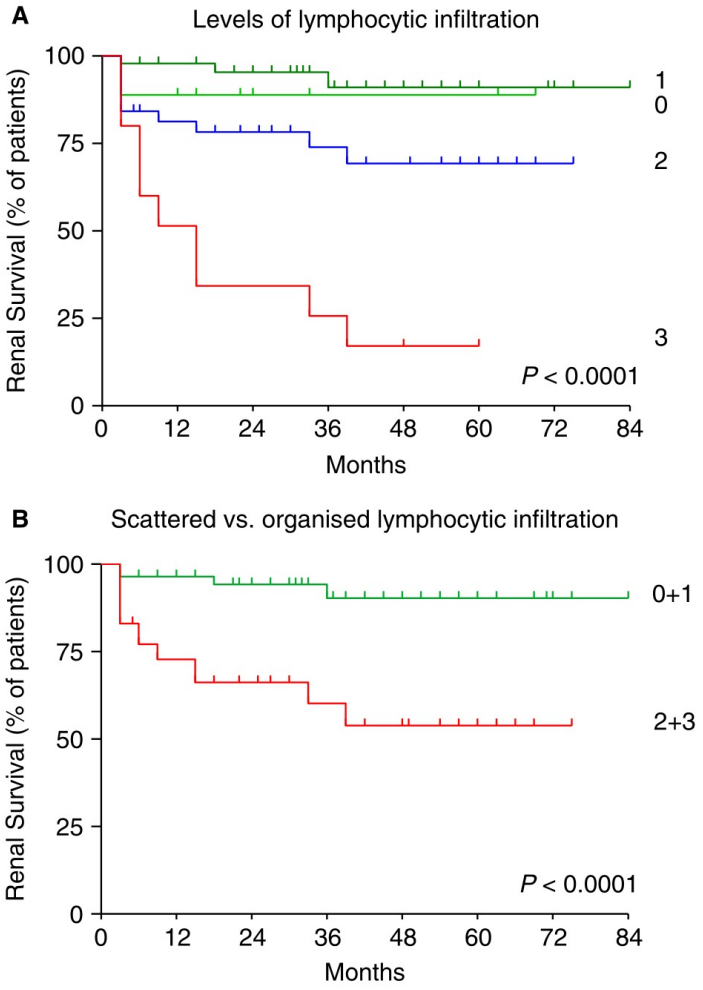
Apport pronostique PBR dans AAV

Infiltrat inflammatoire interstitiel
Organisation en follicules lymphoides



E

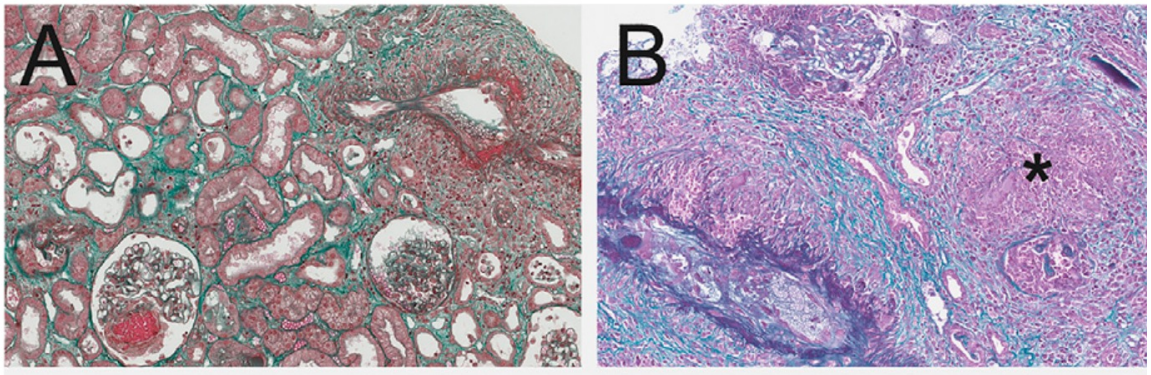
Level	B Cell Infiltrate	*n*
0	None	10
1	Scattered	49
2	Clustered	38
3	Nodular	15



Brix Histopathol 2018

Apport pronostique PBR dans AAV

Artérite : 13% à 20% patients



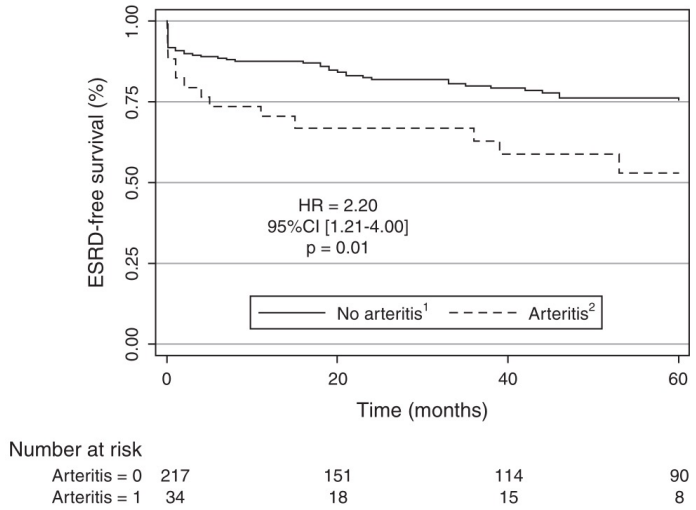
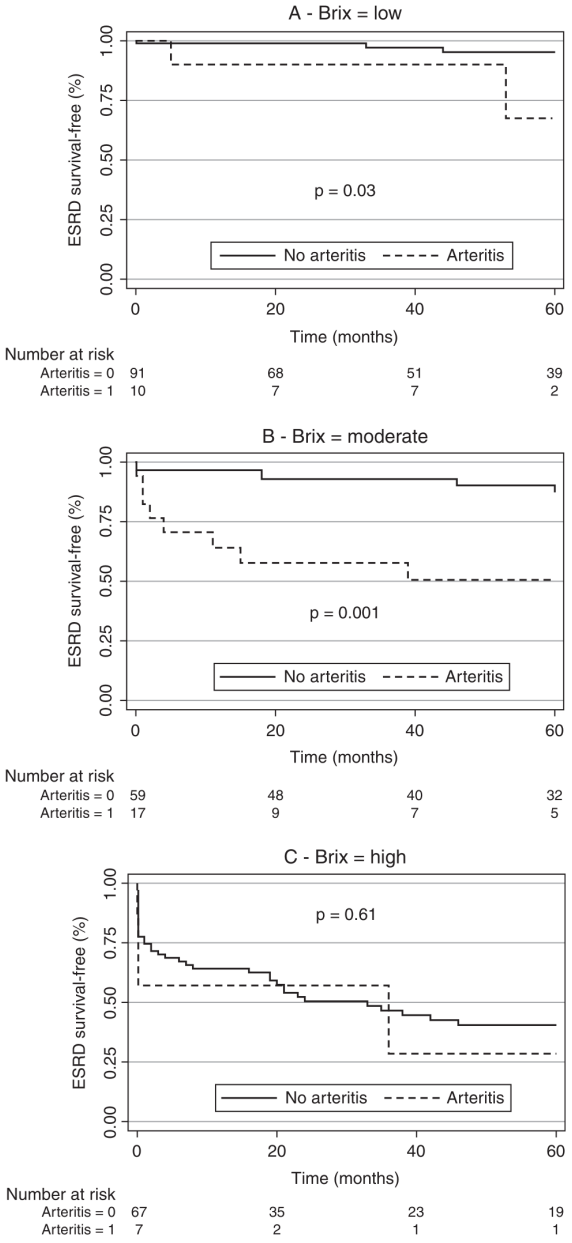


Figure 2. ESKD-free survival of patients with ANCA-associated vasculitis with or without arteritis on index KB. [1]Follow-up time: 42 (IQR, 16–95) months for patients with AAV without arteritis; [2]follow-up time 34 (IQR, 5–55) months for patients with AAV and arteritis. Kaplan–Meier curves, univariable Cox model.

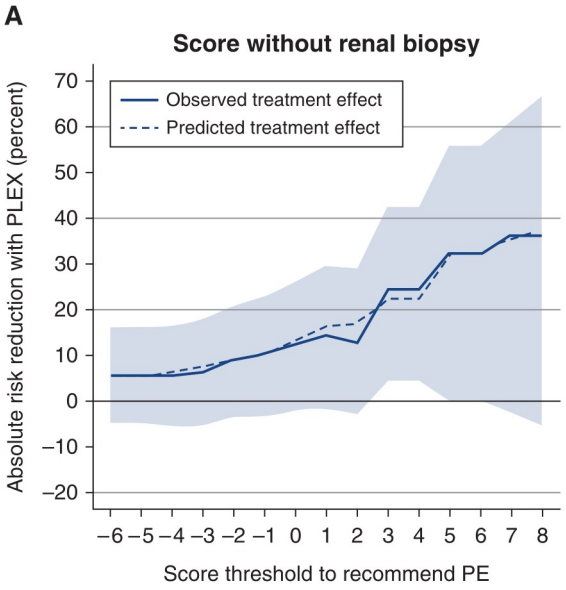


Boudhabhay, JASN 2021

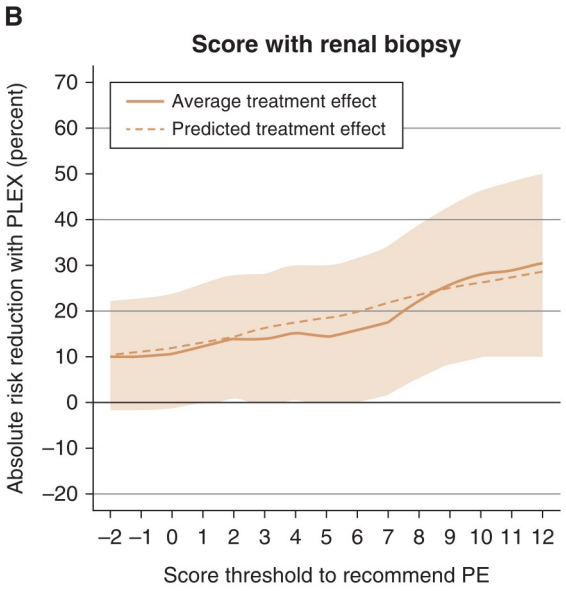
Aide décision thérapeutique

Critères des patients bénéficiant PLEX :

Microscopic polyangiitis,
MPO-ANCA,
higher serum creatinine,
crescentic and sclerotic classes,
higher Brix score



Variable	Score points
Age >45 y	–2
MPA vasculitis	2
PR3 positive	–5
MPO positive	–2
Serum creatinine	
251...400 μmol/L	4
401...600 μmol/L	6
>600 μmol/L	11



Variable	Score points
Male sex	1
MPA	5
RLV	3
PR3 positive	–10
MPO positive	–3
Serum creatinine	
251...400 μmol/L	5
401...600 μmol/L	8
>600 μmol/L	16
Brix score ≥ 7	1
Berden score	
Crescentic	6
Mixed	–8

Nezam JASN 2022

Aide à la décision thérapeutique

101 patients

Post-treatment parameters*			
Serum creatinine, per mg/dL	4.707	2.702-8.199	<0.001
Estimated GFR, per 10ml/min/m^2	0.592	0.466-0.751	<0.001
Proteinuria, per g/g	2.285	1.660-3.145	<0.001
Persistent hematuria, vs not	1.563	0.634-3.855	0.332

* Note. Post-treatment parameters were only evaluated in patients with functional kidneys at 6 months.

Table 4. Nested Cox regression models to evaluate the predictive performance of the AKRiS score at different time intervals

		Time to kidney failure (intervals)				
Model parameters	**Model statistics**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
AKRiS score (*whole cohort*)	Harrell's *C*	0.861 (0.775–0.948)	0.859 (0.785–0.934)	0.854 (0.784–0.926)	0.843 (0.771–0.914)	0.837 (0.766–0.907)
	AIC	151.3	187.2	202.6	219.2	228.7
AKRiS score (*sub-cohort with functional kidneys by 6 months*)	Harrell's *C*	0.782 (0.586–0.906)	0.813 (0.631–0.995)	0.809 (0.650–0.969)	0.786 (0.633–0.938)	0.774 (0.626–0.922)
	AIC	34.2	68.76	84.28	100.8	109.9
AKRiS score + peak recovery eGFR *(whole cohort)*	Harrell's *C*	0.966 (0.927–1.000)	0.955 (0.914–0.999)	0.947 (0.905–0.989)	0.943 (0.902–0.985)	0.927 (0.878–0.976)
	AIC	108.8	138.5	151.7	163.0	184.8
	LR test *P*-value	<0.001	<0.001	<0.001	<0.001	<0.001
AKRiS score + peak recovery eGFR (*sub-cohort with functional kidneys by 6 months*)	Harrell's *C*	0.896 (0.725–0.967)	0.897 (0.780–0.999)	0.887 (0.780–0.994)	0.881 (0.784–0.978)	0.844 (0.730–0.959)
	AIC	29.5	55.72	68.89	80.98	98.42
	LR test *P*-value	<0.001	<0.001	<0.001	<0.001	<0.001

AKRiS: improved ANCA kidney risk score; AIC: Akaike Information Criteria; eGFR: estimated glomerular filtration rate; LR test: likelihood-ratio test.

Sandino-Bermudez Rheumatology 2024

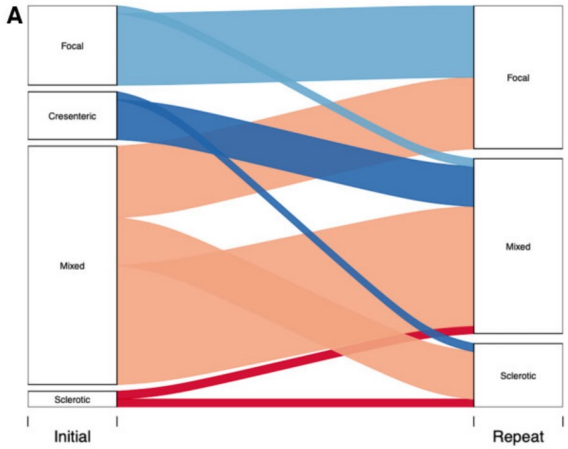
Aide décision thérapeutique

Diagnostic rechute / PBR intervalle

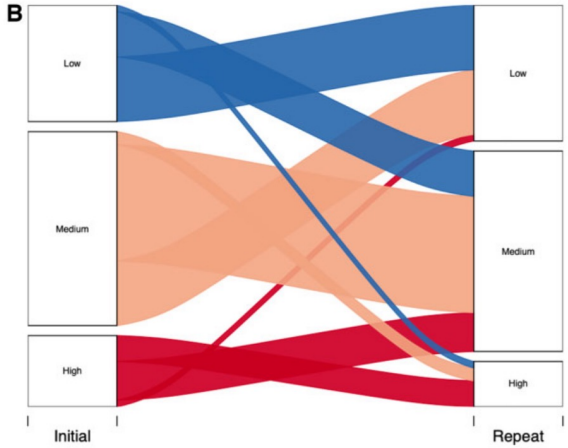
Moins d'activité et plus de chronicité

218 patients
Biopsie intervallaire = 57

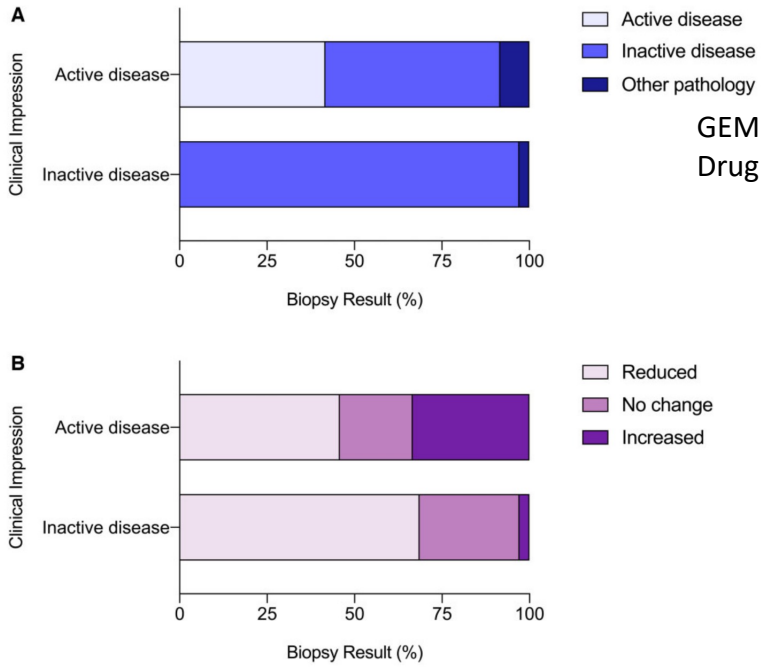
Berden



RRS



Confirmation impression clinique d'activité dans 42%



Chapman Rheumatology 2022

Conclusion : PBR dans AAV

Apport diagnostique

certain pour présentation atypique

Apports pronostiques

lésions chroniques

Basée sur

- 2 fragments : MO + IF
- Données cliniques et biologiques

Données importantes du CR PBR dans AAV

Nombre total de glomérules (>10)

Nombre (%) de glomérule normal

Nombre (%) de croissants
- croissants cellulaires et fibro cellulaires
- croissants fibreux

Nombre (%) de pains à cacheter

% FIAT
NTA
Inflammation interstitielle

Vaisseaux : artériosclérose, artérite, MAT

IF