Vascularites à anticorps anti membrane basale glomérulaire

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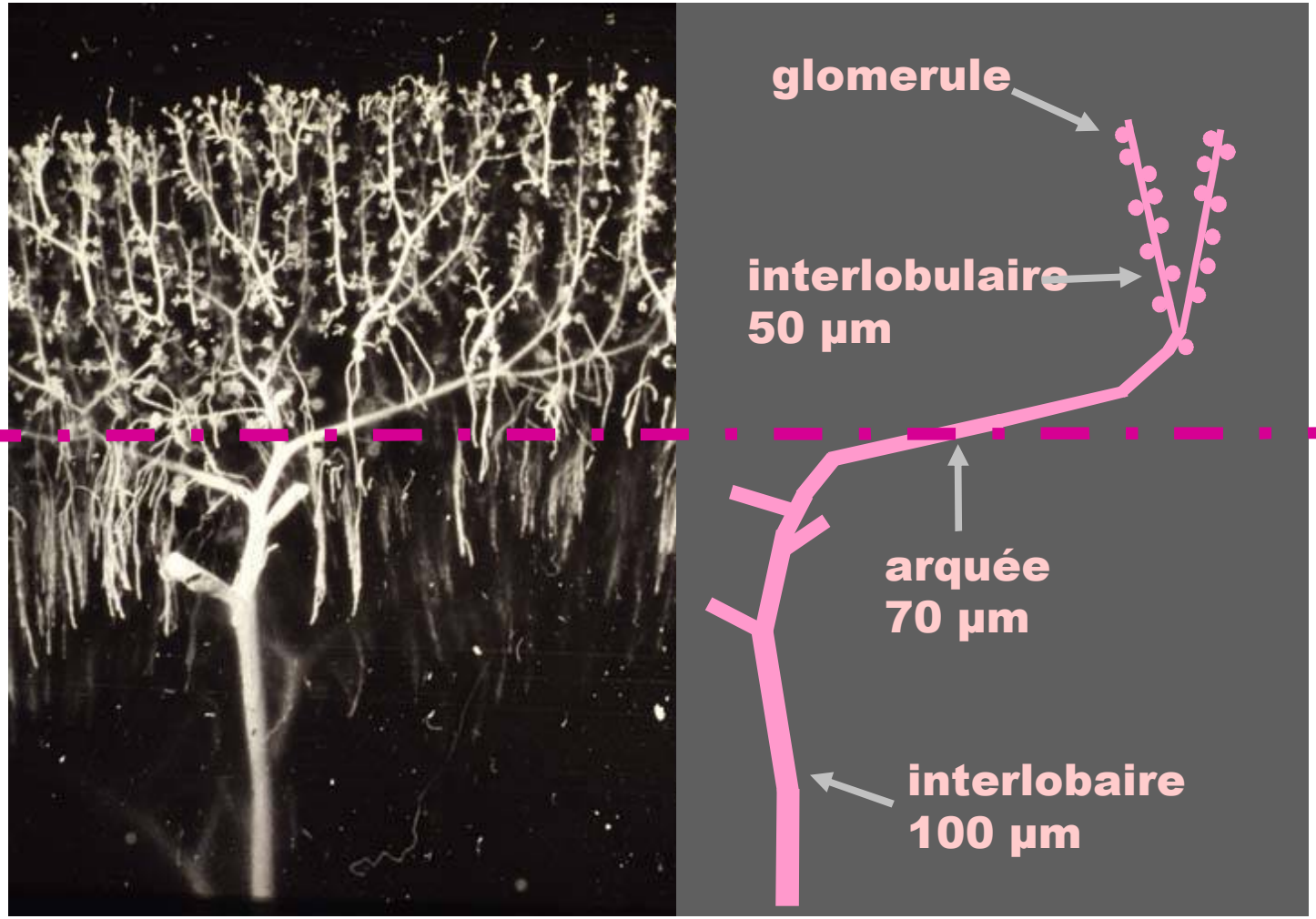
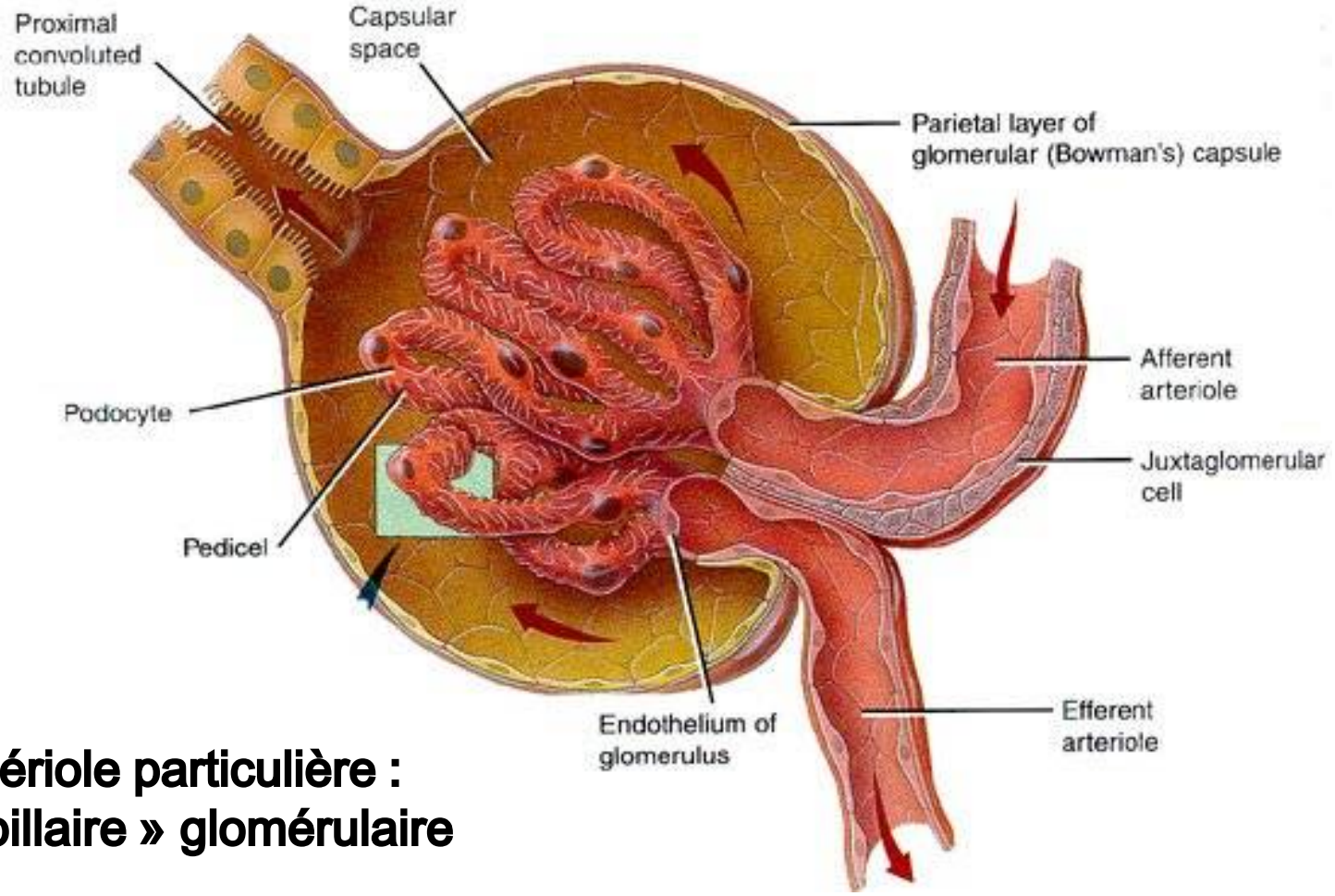
Petits vaisseaux

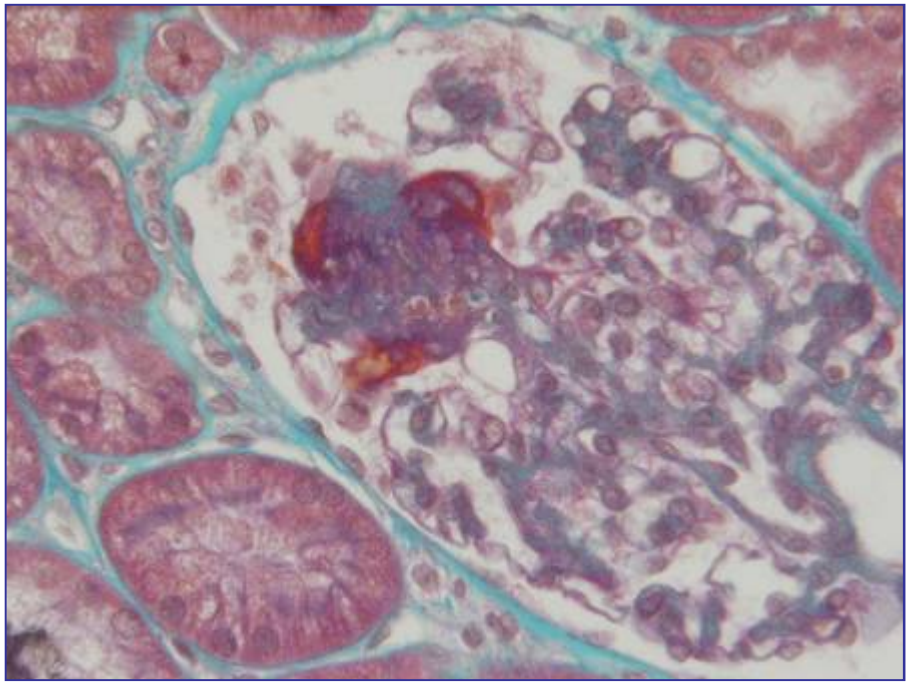


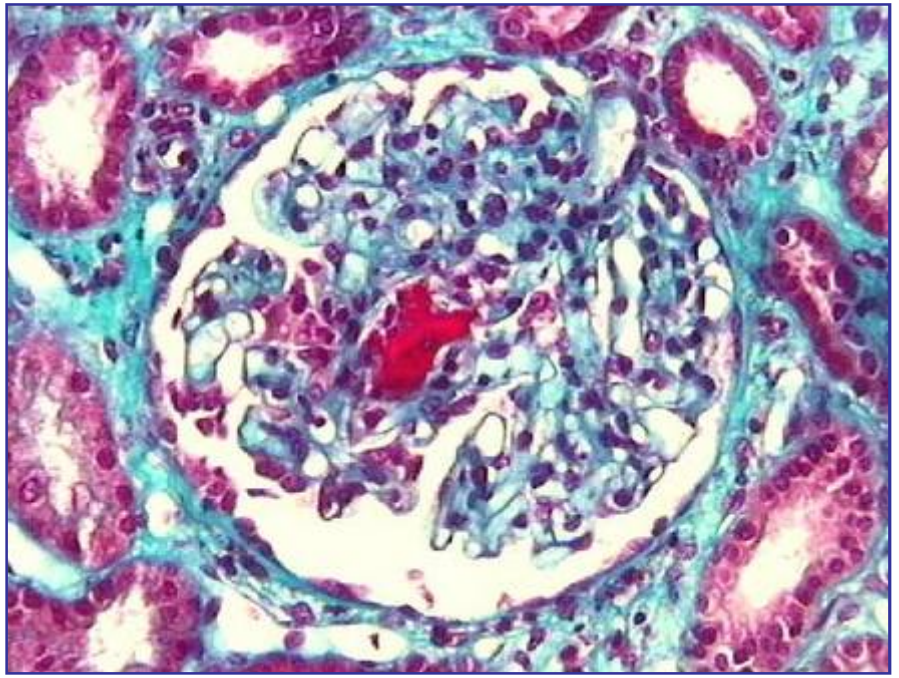
Vascularisation rénale



Une artériole particulière :
le « capillaire » glomérulaire

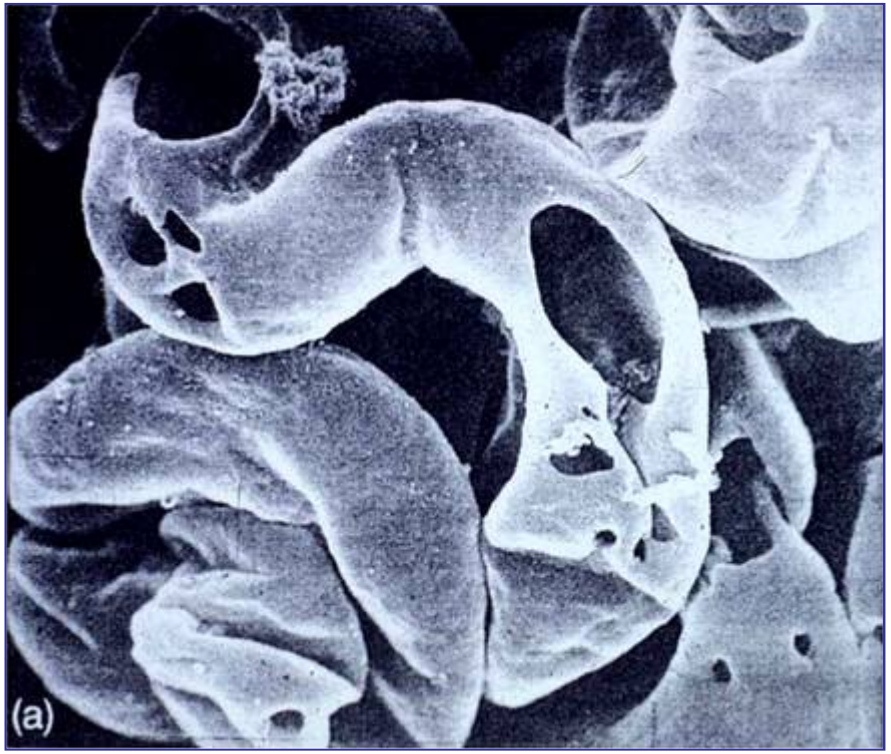
Vascularite rénale
Atteinte des artérioles glomérulaires





Nécrose fibrinoïde glomérulaire

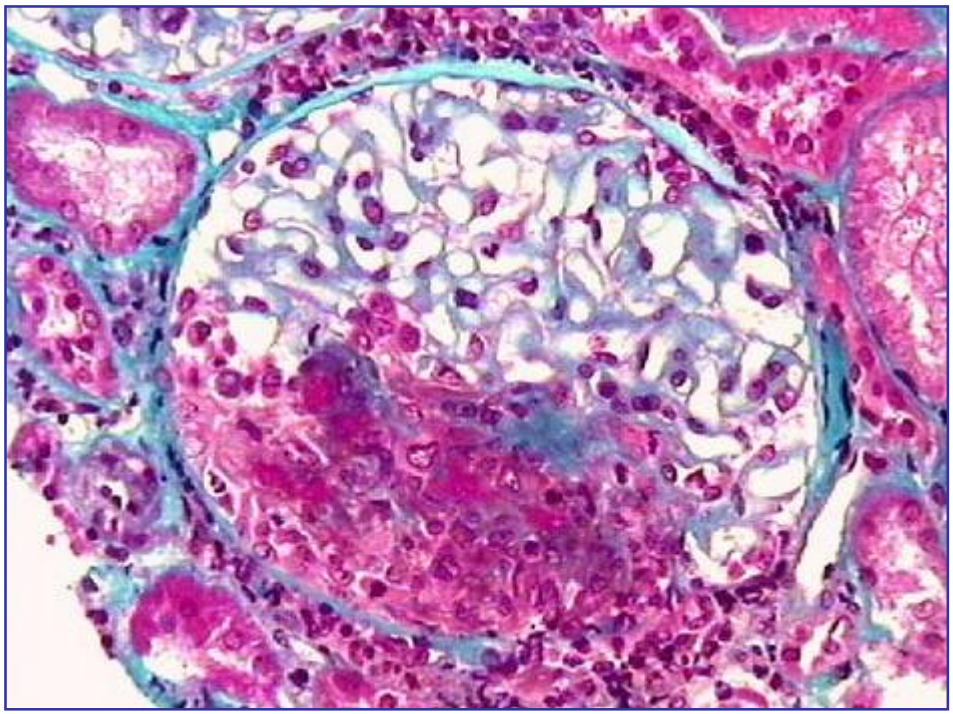
Vascularite rénale
Atteinte des artérioles glomérulaires



La rupture de la MBG conduit à la libération de médiateurs de l' inflammation qui vont agir sur les cellules épithéliales glomérulaires

Formation du croissant (prolifération extracapillaire)

Vascularite rénale
Atteinte des artérioles glomérulaires



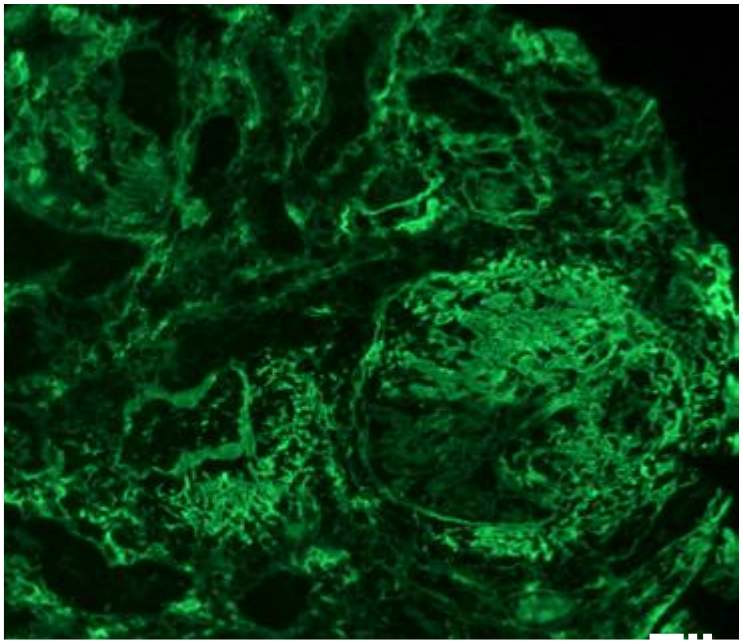
La rupture de la MBG conduit à la libération de médiateurs de l'inflammation qui vont agir sur les cellules épithéliales glomérulaires

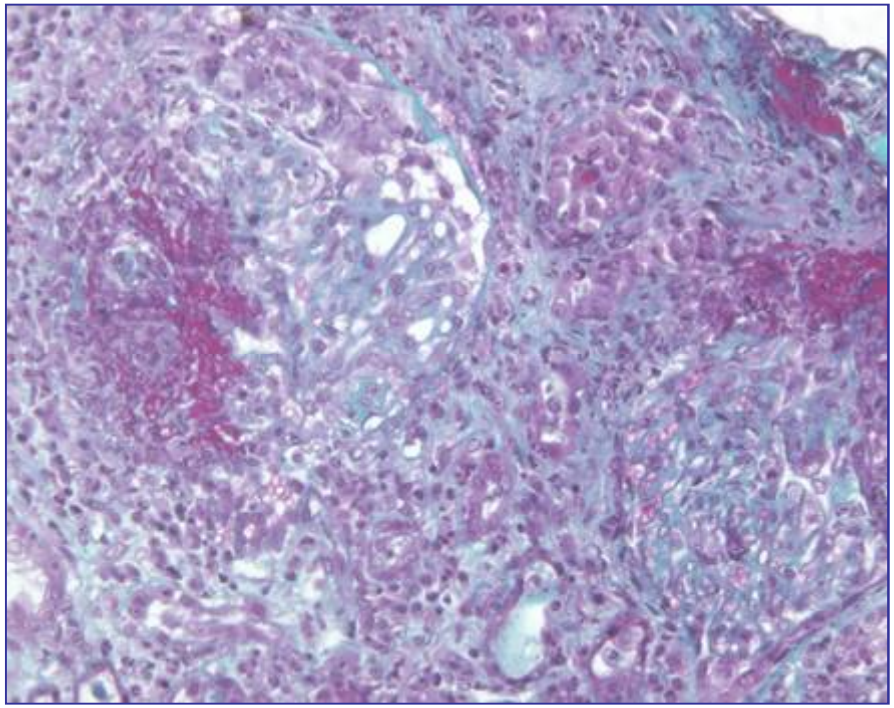
⬇

Formation du croissant (prolifération extracapillaire)

Vascularite rénale
Atteinte des artérioles glomérulaires

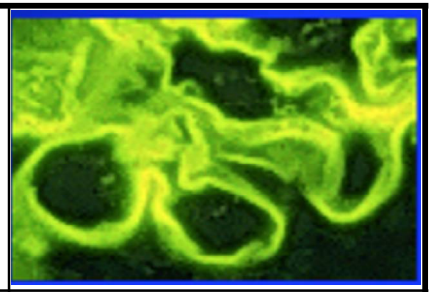
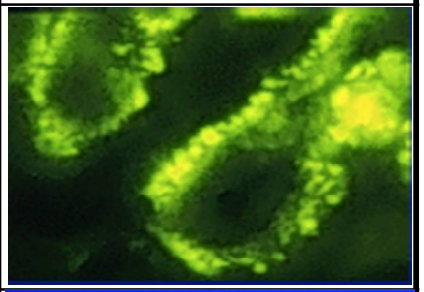
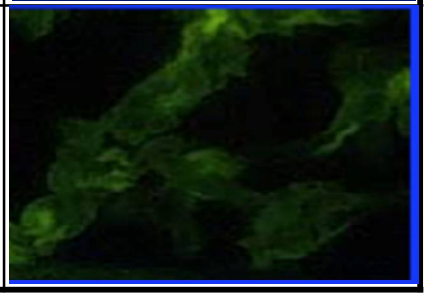
Le diagnostic étiologique devant une GN extracapillaire repose sur l'analyse des dépôts immuns en IF





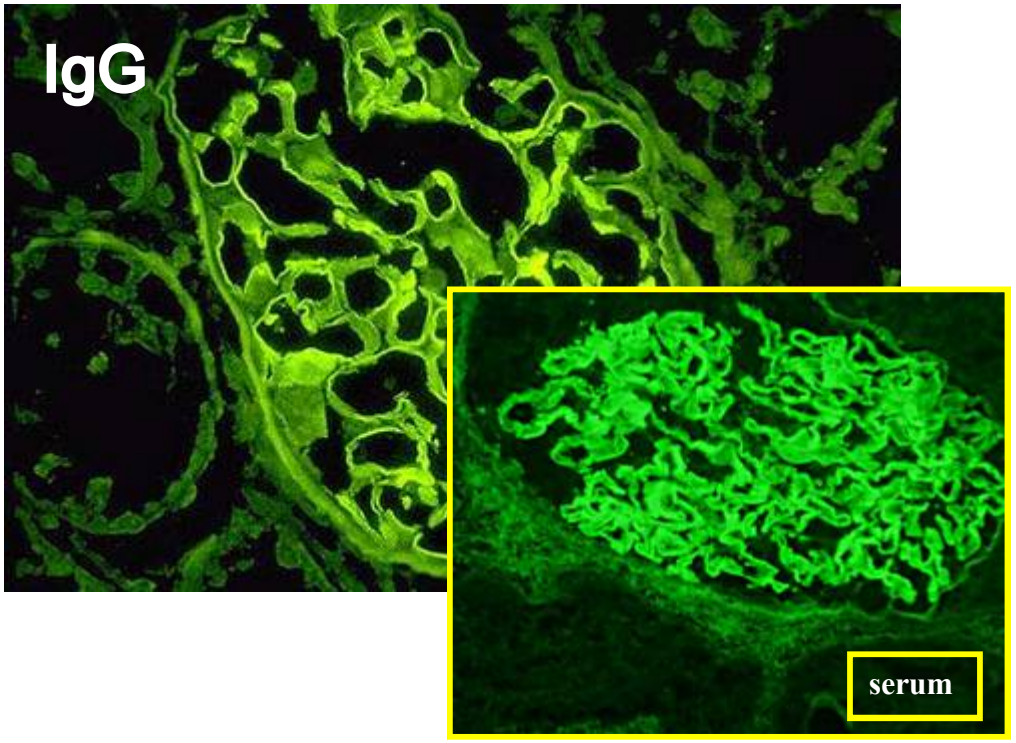
Immunofluorescence

Dépôts d'Ig et de fraction du complément

Dépôts d'ac anti-MBG	Dépôts linéraies d'igG sur MBG	
Dépôts de CIC	Dépôts granuleux Ig et/ou complément	
Absence de dépôts (pauci-immunes)	Pas de dépôts d'Ig mais fibrine dans croissant et nécrose	

Vascularite rénale
Atteinte des artérioles glomérulaires

Le diagnostic étiologique devant une GN extracapillaire repose sur l'analyse des dépôts immuns en IF



Dépôts linéaires d'IgG =

Vascularite secondaire à un Ac anti-MBG

Définition

- Vascularite avec anticorps antimembrane basale glomérulaire : atteinte rénale isolée

- Maladie de Goodpasture :
  - Vascularite avec anticorps antimembrane basale glomérulaire associée à une hémorragie intra-alvéolaire

these cases, while bearing in mind the possibility of their being distinct infectious diseases of the nervous system, which may escape detection because of a general similarity in their clinical manifestations to well-recognized entities does not aid in establishing lethargic encephalitis as a definite clinical entity.

THE SIGNIFICANCE OF CERTAIN PULMONARY LESIONS IN RELATION TO THE ETIOLOGY OF INFLUENZA.

By Ernest W. Goodpasture, M.D.,
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Goodpasture E: Am J Med Sci 158:863–870, 1919
Stanton MC, Tange JD. Aust N Z J Med 7:132–144, 1958

Physiopathologie
Rôle des anti-GBM

THE ROLE OF ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY IN THE PATHOGENESIS OF HUMAN GLOMERULONEPHRITIS*

By R. A. LERNER, M.D., R. J. GLASSOCK,‡ M.D., AND FRANK J. DIXON, M.D.

(From the Department of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, California 92037,§ and the Cardiorenal Section, Peter Bent Brigham Hospital, Harvard Medical School, Boston, Massachusetts 02115‖)¶

PLATES 72–76

(Received for publication 5 July 1967)

The concept that anti-glomerular antibodies might cause glomerulonephritis dates back to the beginning of this century, when Lindemann demonstrated the nephritogenic properties of heterologous anti-kidney antibodies (1). Subsequent work on nephrotoxic serum nephritis has provided precise information concerning the nature and potency of these heterologous nephritogenic antibodies, the location and immunochemical characteristics of the glomerular antigen, and some of the mediators of inflammation activated by the antibody-antigen interaction (reviewed in reference 2). A further step toward implicating this pathogenetic mechanism in nephritis was achieved when it was shown that animals immunized with homologous or heterologous glomerular basement membranes (GBM) could develop glomerulonephritis (3, 4). The demonstration of anti-GBM antibody in the serum and kidneys of such animals and the passive serum transfer of this form of nephritis in sheep (5) and rabbits (6) to normal homologous recipients provided definitive evidence that an animal could, upon appropriate immunization, form nephritogenic anti-GBM antibodies apparently capable of producing an autoimmune glomerulonephritis.

Lerner RA, Glassock RJ, Dixon FJ.. J Exp Med 1967; 126:989-1004.

Caractérisation anti GBM

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 263, No. 26, Issue of September 15, pp. 13374–13380, 1988
Printed in U.S.A.

Identification of the Goodpasture Antigen as the α3(IV) Chain of Collagen IV*

(Received for publication, March 25, 1988)

Juan Saus‡§, Jorgen Wieslander¶, Jan P. M. Langeveld‖, Susan Quinones‡, and Billy G. Hudson‖

From the ‖Department of Biochemistry, University of Kansas Medical Center, Kansas City, Kansas, 66103, the ‡Department of Medicine, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey, 08854, and the ¶Department of Biochemistry, BioCarb, S-223 70, Lund, Sweden

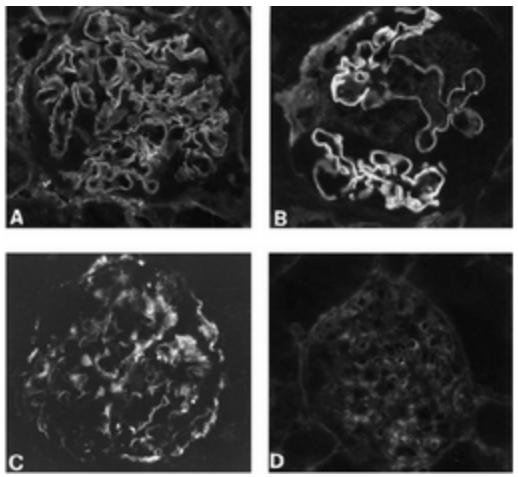
Saus J, Wieslander J, Langeveld JP, J Biol Chem 1988;263:13374-80.
Butkowski RJ, Langeveld JP, Wieslander J Biol Chem 1987;262:7874-7.
Turner N, Mason PJ, Brown R, et al. J Clin Invest 1992;89:592-601.

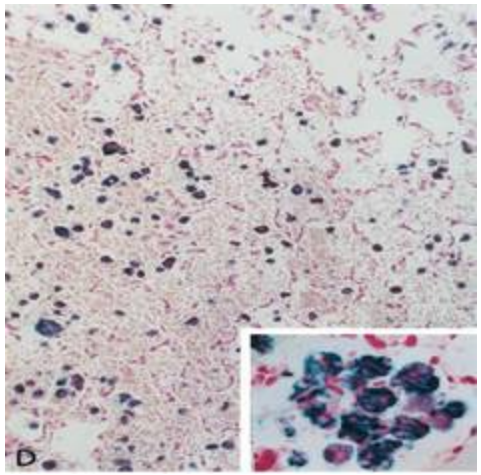
Rôle pathogène

Kidney International, Vol. 54 (1998), pp. 1550–1561

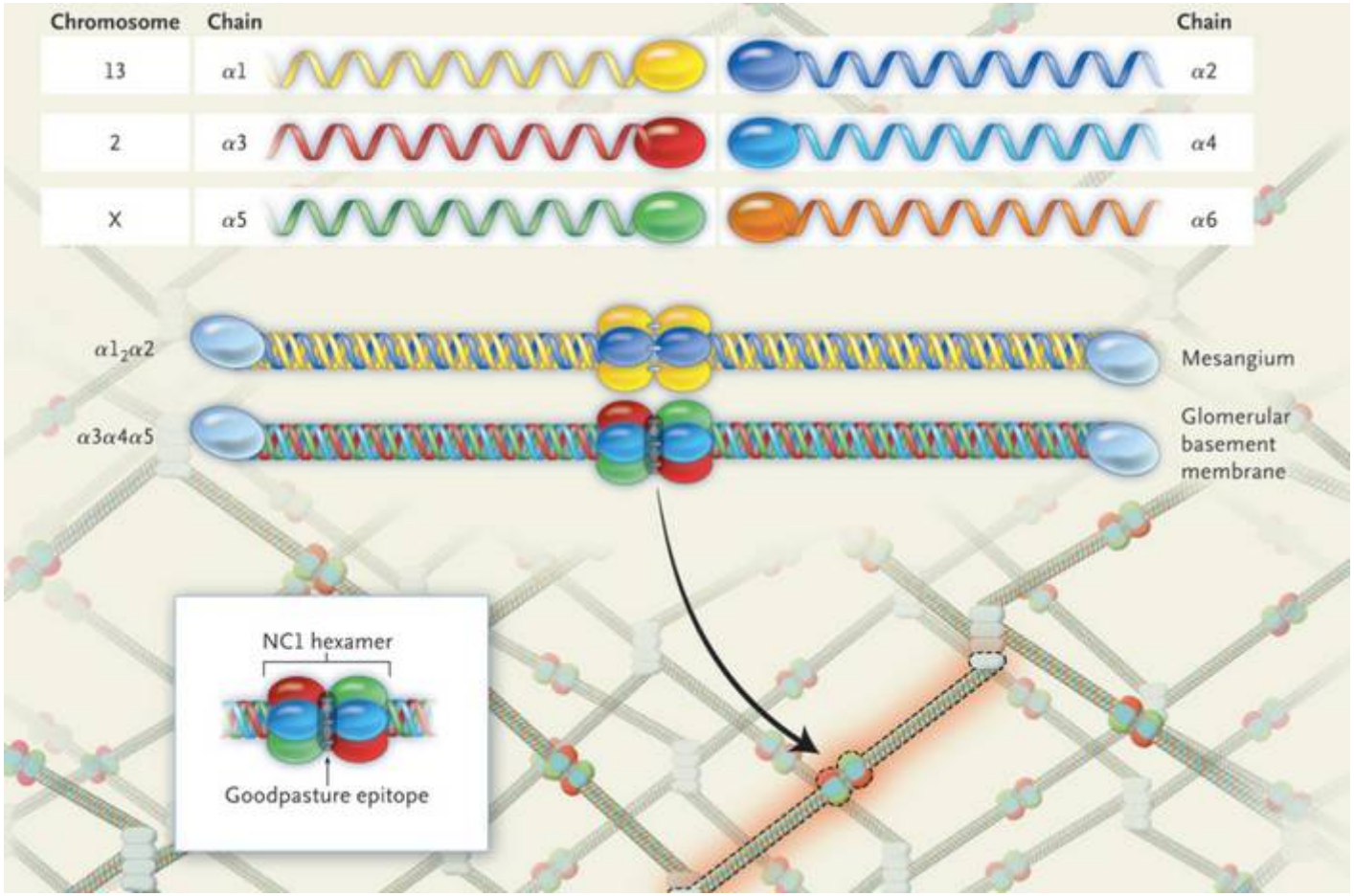
Experimental Goodpasture's syndrome in Wistar-Kyoto rats immunized with α3 chain of type IV collagen

MAURO ABBATE, RAGHURAM KALLURI,[1] DANIELA CORNA, NAOTO YAMAGUCHI, ROBERT T. MCCLUSKEY, BILLY G. HUDSON, GIUSEPPE ANDRES, CARLA ZOJA, and GIUSEPPE REMUZZI



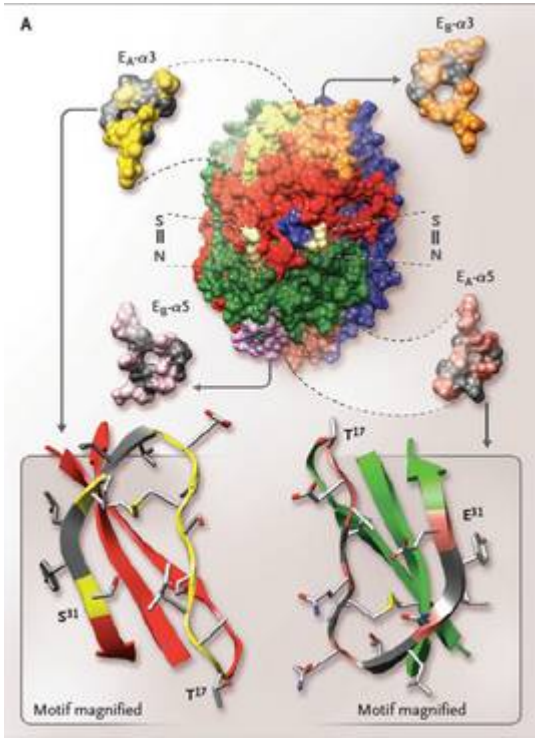


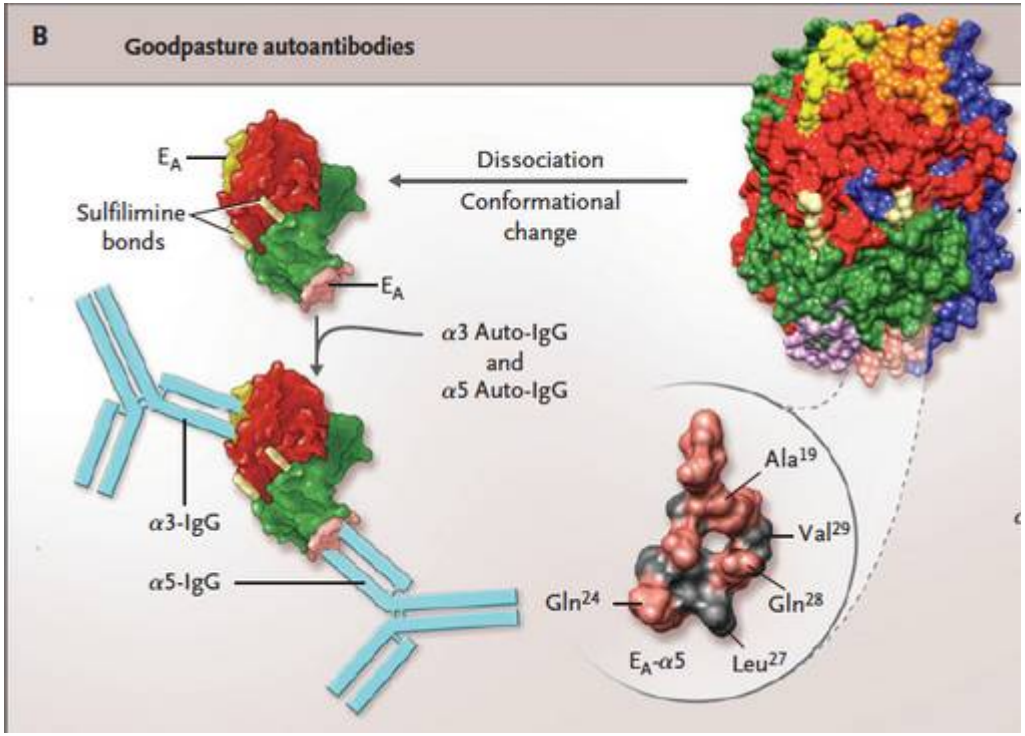
Caractérisation de l'antigène



Pedchenko V, Bondar O, Fogo AB, et al..N Engl J Med 2010;363:343-54.

Typage de l'antigène





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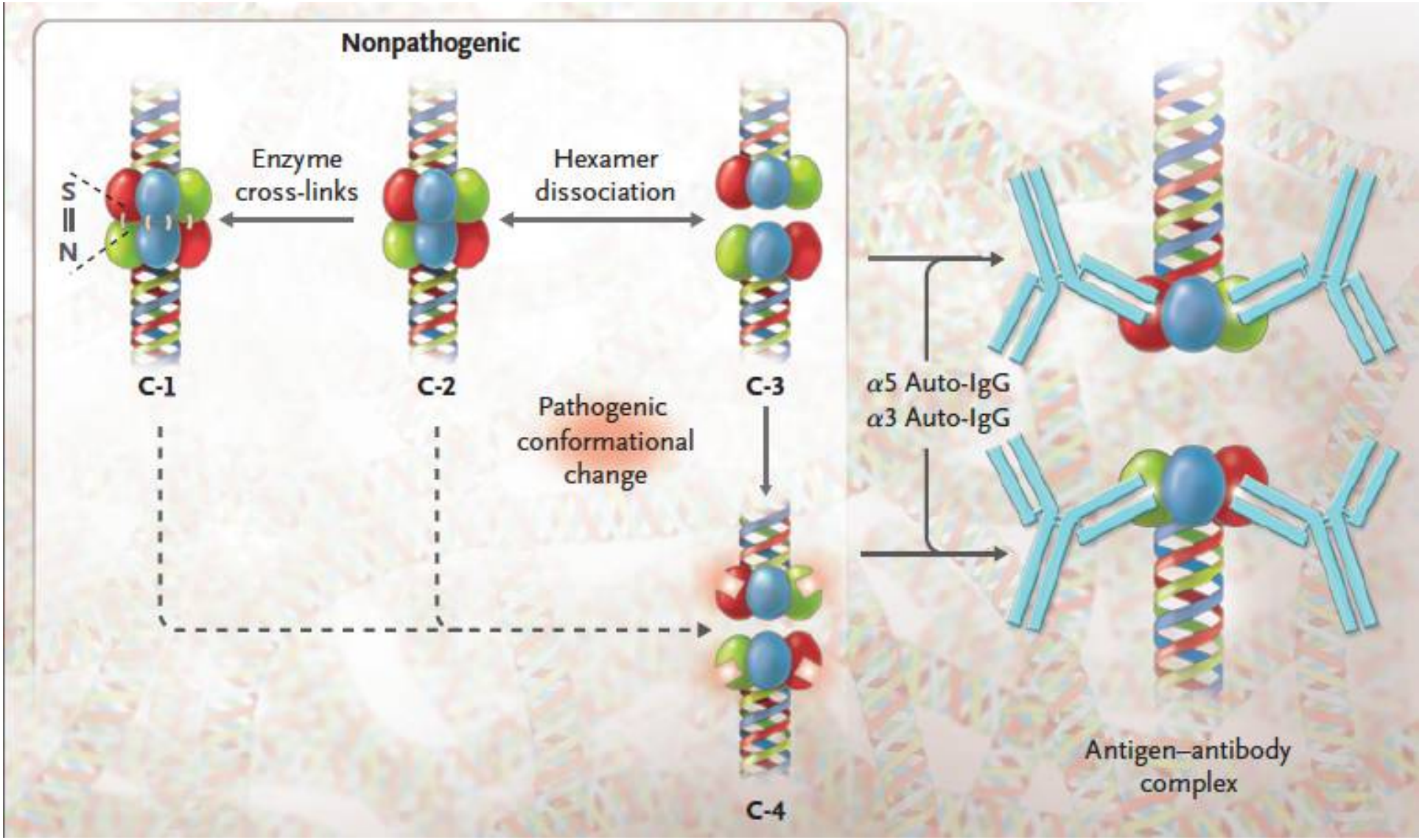
Nonpathogenic
S
N
Enzyme cross-links
Hexamer dissociation
C-1
C-2
C-3
Pathogenic conformational change
C-4
α5 Auto-IgG
α3 Auto-IgG
Antigen–antibody complex

Autres

- Rôle de l'immunité cellulaire
  - Transfert de cellule T anti-collagène IV NC1 (Wu, JCI 2002)
- Rôle des Fcγrecepteur
  - Polymorphisme de copie de Fcγr3 (Aitman, Nature 2006)
  - FcγR2b$^{-/-}$ et immunisation NC1/IV (Nakamura, JExMed, 2000)
- Rôle du complément
  - Souris déficiente en C3/C4 (Sheerin, Clin Exp Immunol 1997)

Facteurs favorisants

- Infections
- Toxiques
- Génétique

Infection

these cases, while bearing in mind the possibility of their being distinct infectious diseases of the nervous system, which may escape detection because of a general similarity in their clinical manifestations to well-recognized entities does not aid in establishing lethargic encephalitis as a definite clinical entity.

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Goodpasture E: Am J Med Sci 158:863–870, 1919

Toxique

- Tabac
- Hydrocarbure
- Lithotritie
- Alemtuzumab
- …

Génétique

- Association forte avec HLA DR2 : 80 %
- Association avec HLA DRB1*1501 and 1502
- Meta-analyse :
  - HLA DRB1*1501
  - DRB1*04 and DRB1*03
  - Fréquence diminuée de DRB1*07 and DRB1*01.
  - Fréquence augmentée de DQB1*06

Clinique

- Incidence bimodale : 0,5 à 1,8 cas / 10^6
  - 3eme et 6eme décennie
  - Légère prédominance masculine
- Formes rénales isolées : 30 à 40 % des cas
- Atteintes rénales
  - 1 à 5 % des GN
  - 10 à 20 % des GN à croissant

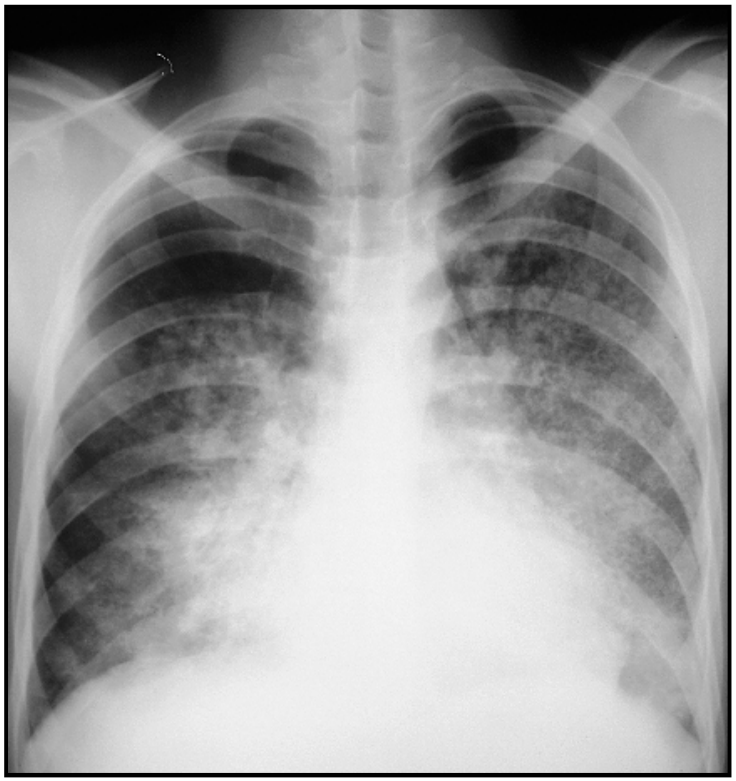
Signes cliniques

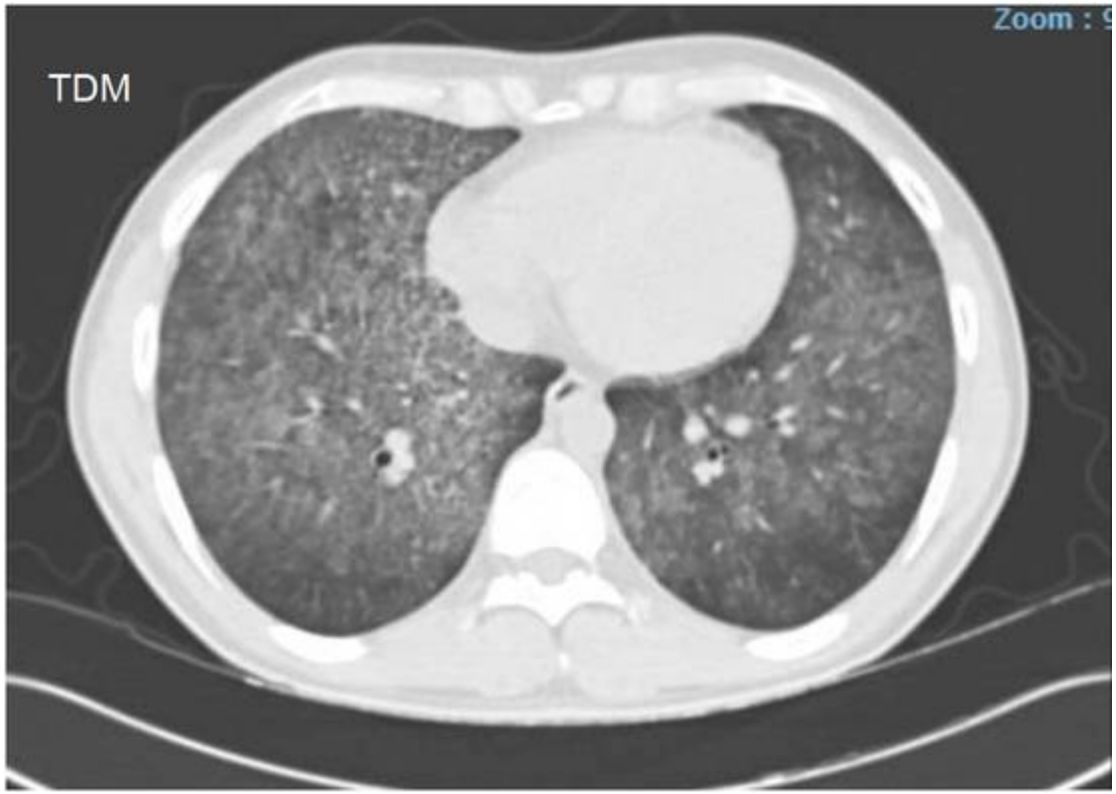
- Insuffisance rénale
  - HTA tardive
- Signes pulmonaires (37 %)
  - Dyspnée
  - Hémoptysie
- Signes généraux
- Autres (articulaires etc…)
  - Recherche d'une positivité des ANCA

Signes biologiques

- GNRP
  - Hématurie
- Imagerie thoracique
  - Radio
  - TDM
- Recherche d'anticorps anti GBM

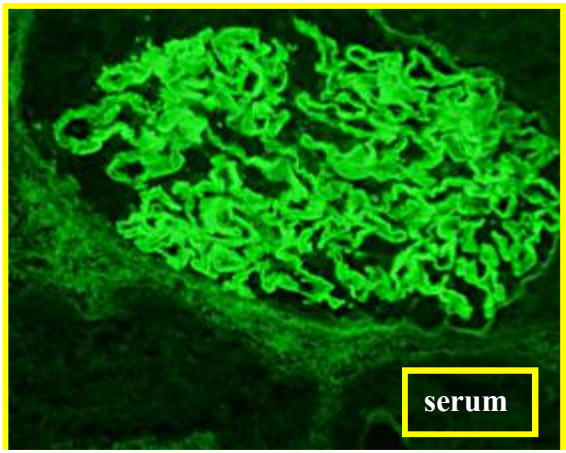
Atteinte pulmonaire



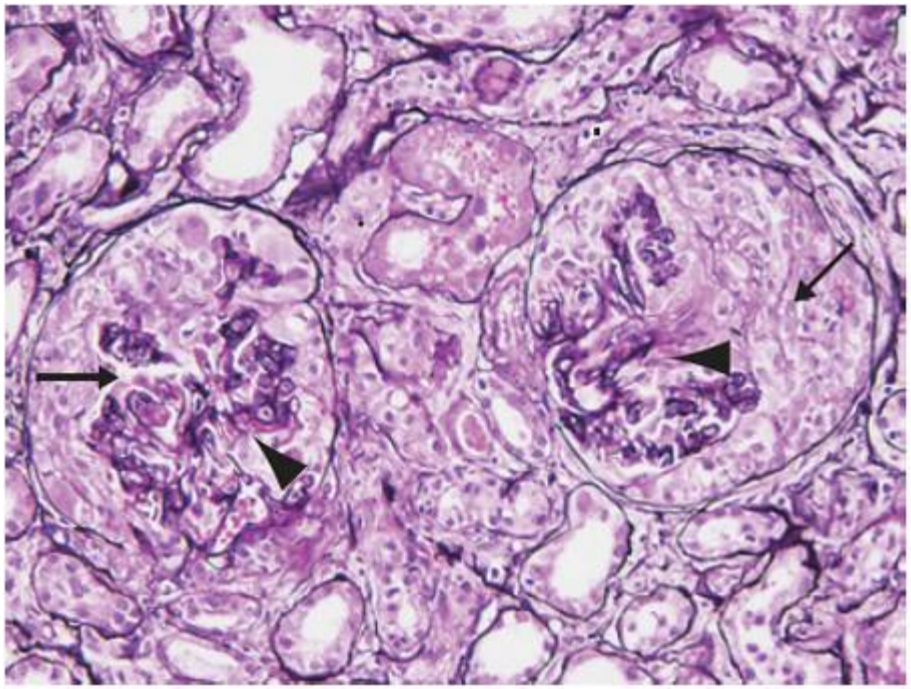


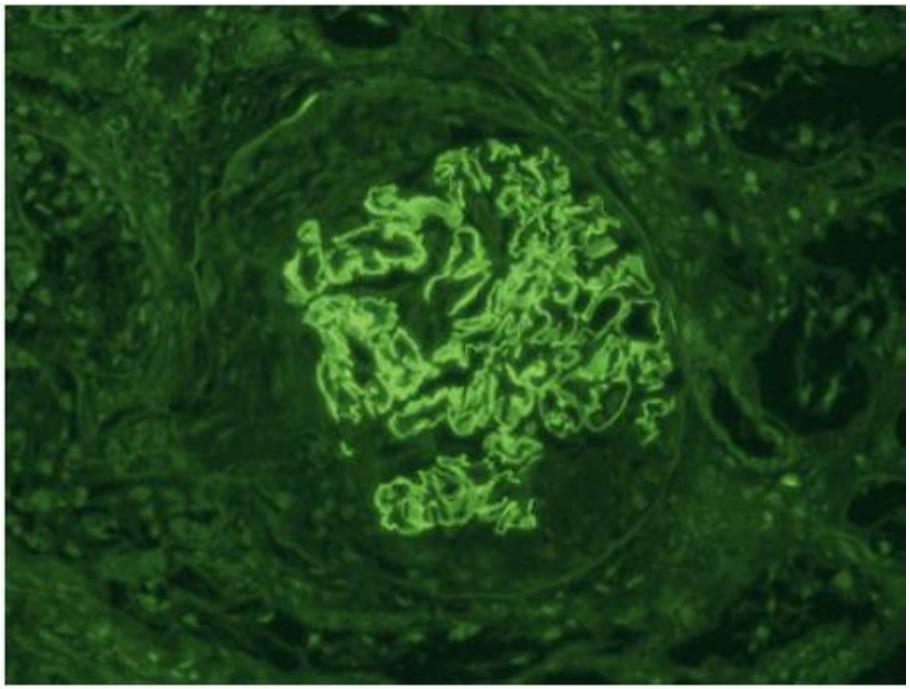
Recherche d'anticorps antiGBM

- Détection par ELISA :
  - GBM purifié bovin ou mouton
  - Enrichi pour le domaine NC1 de chaine α3Col4
- Test par Western blot
- Dépôt sur coupe de rein de singe en IF

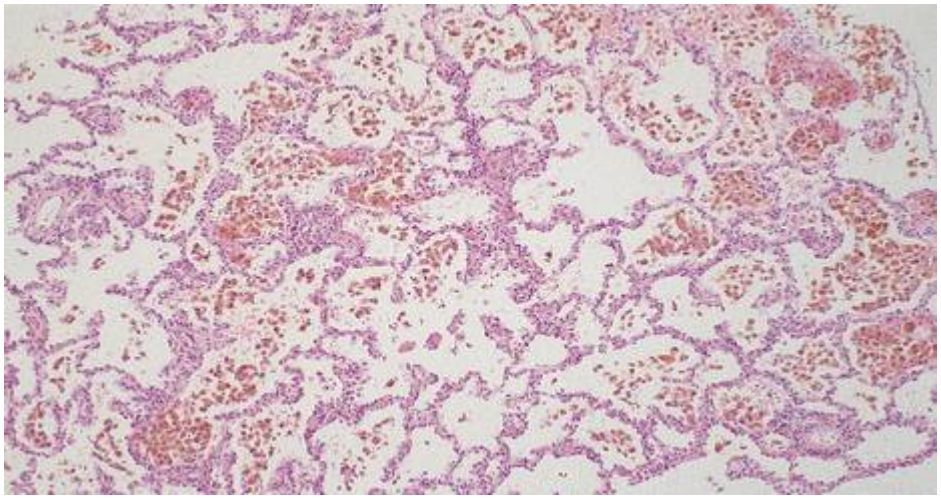


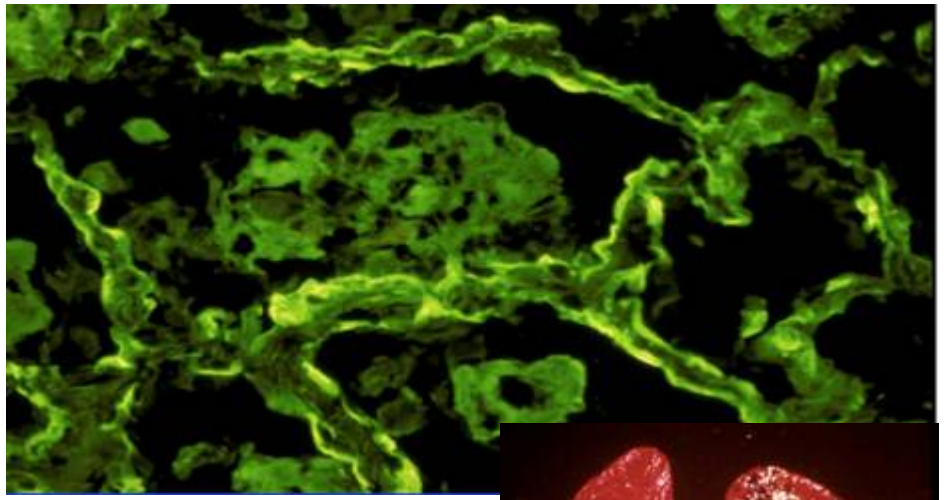
Biopsie rénale

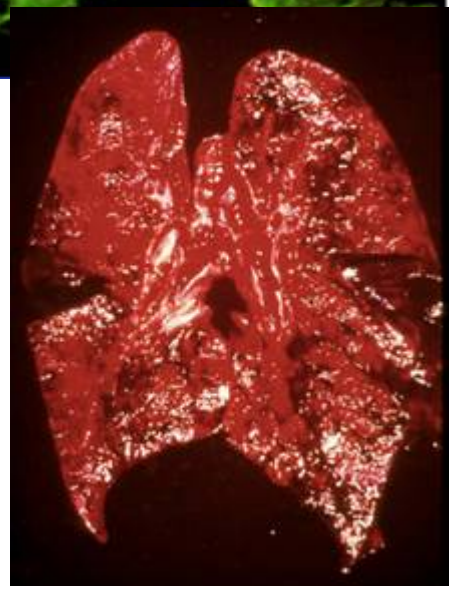




Atteinte pulmonaire







- Alvéolite hémorragique diffuse
- Pneumocytes turgescents
- Hématies
- Macrophages avec hémosidérine

Pronostic

- Vital : pulmonaire
- Fonctionnel : rénal
  - Dialyse à la présentation
  - % de glomérules atteints (85 % à 100 % si dialyse)
- Pas ou peu de rechutes

Principe du Traitement

- Urgence thérapeutique en cas de confirmation et/ou hautement suspect
- Pas de traitement d'entretien
- Transplantation rénale quand anti GBM négatif pendant 6 mois

Type de Traitement Indication

- Immunosuppression
  - Cyclophosphamide
  - Corticostéroïdes
- Plasmaphérèses
- Tous les patients sauf
  - Dialyse à la présentation
  - 100 % de croissants sur la biopsie rénale
  - Absence d'hémorragie pulmonaire

Modalités de traitement

Initial	
Plasma exchange	Daily, 4 L exchange for 5% human albumin solution; use 300 to 600 mL fresh frozen plasma within 3 days of any invasive procedure (e.g., biopsy) or in patients with pulmonary hemorrhage; continue for 14 days or until antibody levels are fully suppressed; withhold if platelet count $<70 \times 10^9$/mL, or hemoglobin <9 g/dL; watch for coagulopathy, hypocalcemia, and hypokalemia
Cyclophosphamide	Oral dosing at 2 to 3 mg/kg/day (round down to nearest 50 mg; reduce to 2 mg/kg/day in patients over 55 years); stop if white cell count $<4 \times 10^9$/mL and restart at lower dose when counts $>4 \times 10^9$/mL
Prednisolone	Oral dosing at 1 mg/kg/day (maximum 60 mg); reduce dose weekly to 20 mg by week 6 and then more slowly; no evidence for benefit of intravenous methylprednisolone and can increase infection risk (possibly use if plasma exchange not available)
Prophylactic treatments	Oral nystatin and amphotericin (or fluconazole) for oropharyngeal fungus infection; ranitidine or proton-pump inhibitor for steroid-promoted gastric ulceration; low-dose cotrimoxazole for *Pneumocystis carinii* pneumonia prevention; consider acyclovir as cytomegalovirus prophylaxis; consider calcium/vitamin D for prevention of osteoporosis (but relatively short course of steroids)
Maintenance	
Prednisolone	Reduce dose slowly from 20 mg at 6 weeks; stop completely by 6 months
Cyclophosphamide	Stop after 2 to 3 months; no further cytotoxic agents necessary

Rituximab?

Journal of Autoimmunity xxx (2015) 1–6

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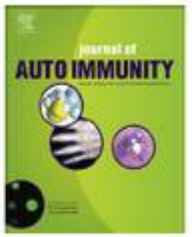
journal homepage: www.elsevier.com/locate/jautimm



Forum

Rituximab in anti-GBM disease: A retrospective study of 8 patients

Maxime Touzot [a, *], Johanne Poisson [b], Stanislas Faguer [c], David Ribes [c], Pascal Cohen [d], Loic Geffray [e], Nadia Anguel [f], Helene François [a, h], Alexandre Karras [g], Patrice Cacoub [b, i], Antoine Durrbach [a, h], David Saadoun [b, i, **]

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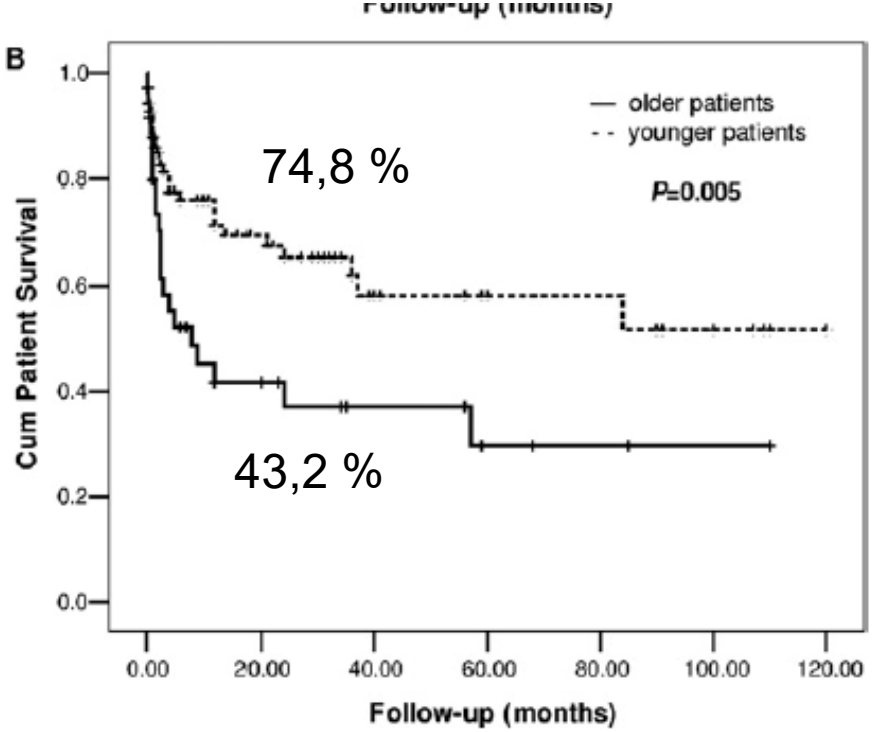
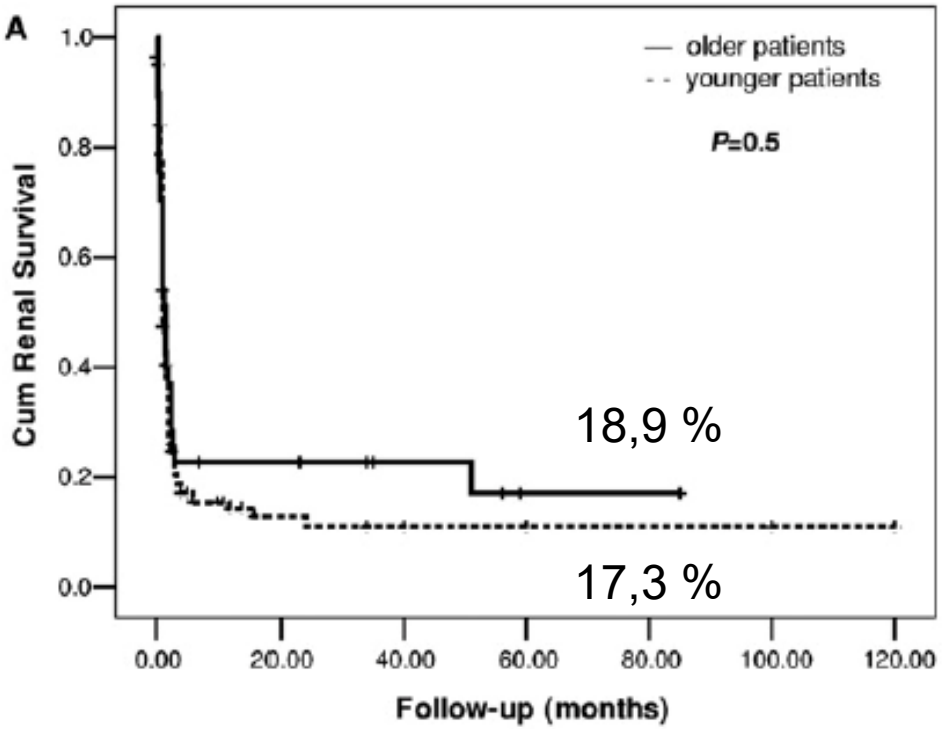
[b] Département de Médecine Interne et d'Immunologie clinique, Groupe Hospitalier Pitié-Salpêtrière, 84, boulevard de l'Hôpital, Paris 75013, France
[c] Département de Néphrologie et Transplantation d'Organes, Centre Hospitalo-Universitaire de Rangueil, Toulouse, France
[d] Service de Médecine interne, groupe hospitalier Cochin, Paris, France
[e] Service de médecine Interne CH lisieux, France
[f] Service de réanimation médicale, CHU Bicêtre, Le Kremlin-Bicêtre, France
[g] Service de néphrologie, hôpital européen Georges-Pompidou, Paris, France
[h] Institut National de la Santé et de la Recherche Médicale INSERM U1014 Villejuif, France
[i] Centre national de référence maladies systémiques et autoimmunes rares, DHU Inflammation, Immunopathologie, Biothérapie, Université Paris VI—Pierre et Marie Curie, Paris, France

Résultats

Survie patients



Survie rénale



Cui Z et al. AJKD 2011;57:575-582.

Devenir en 2017

CJASN ePress. Published on November 21, 2017 as doi: 10.2215/CJN.04290417

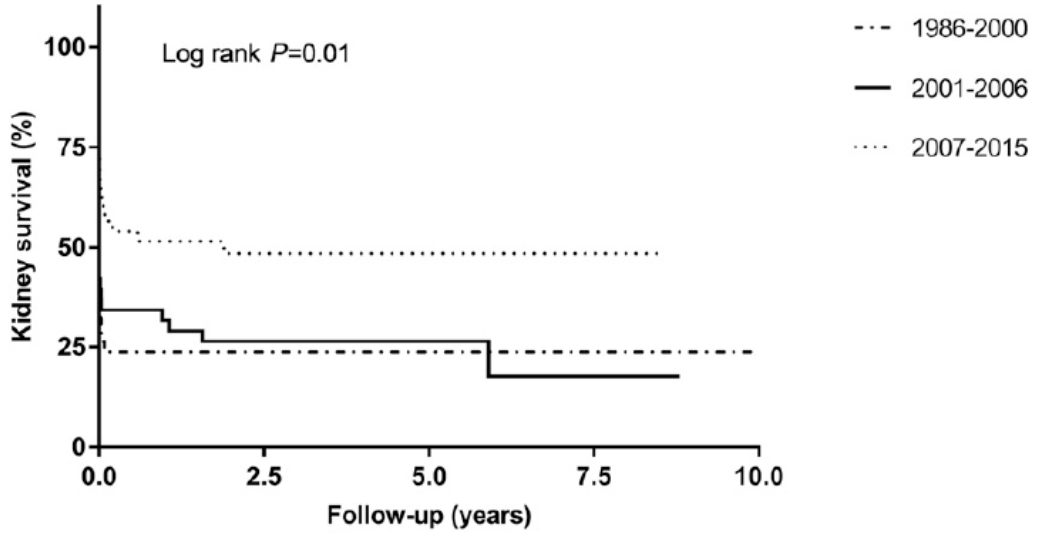
Article

Predicting Outcome in Patients with Anti-GBM Glomerulonephritis

Emma E. van Daalen,[1] J. Charles Jennette,[2] Stephen P. McAdoo,[3] Charles D. Pusey,[3] Marco A. Alba,[2] Caroline J. Poulton,[4] Ron Wolterbeek,[5] Tri Q. Nguyen,[6] Roel Goldschmeding,[6] Bassam Alchi,[8] Meryl Griffiths,[9] Janak R. de Zoysa,[10] Beula Vincent,[10] Jan A. Bruijn,[1] and Ingeborg M. Bajema[1]

Clin J Am Soc Nephrol. 2018 Jan 6;13(1):63-72

Survie rénale



N at risk					
1986 to 2000	41	8	7	5	2
2001 to 2006	38	6	4	2	0
2007 to 2015	44	11	6	2	0

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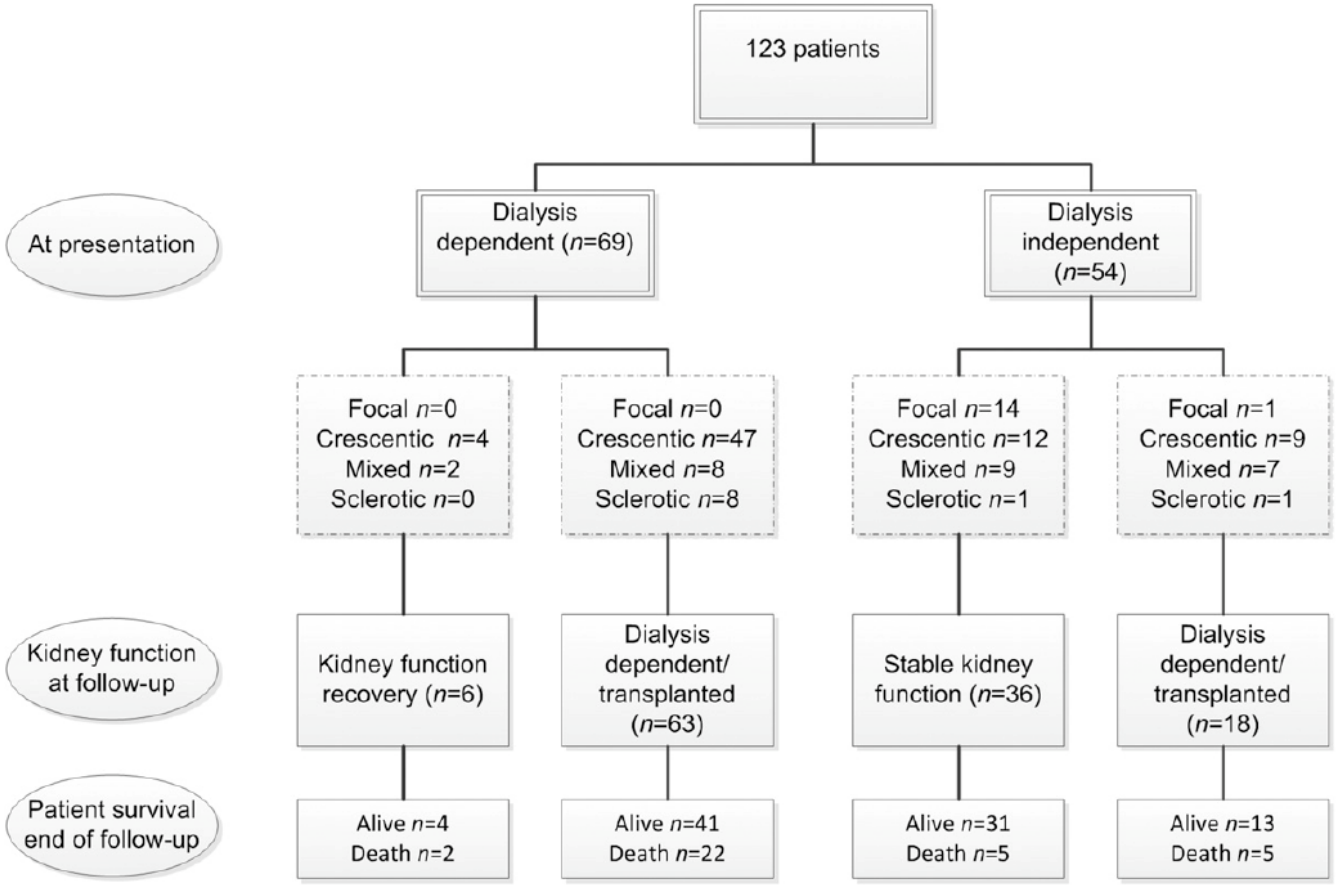
Evaluation



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Facteurs de risque

Table 6. Prognostic significance of clinical and histopathologic parameters on ESRD

Variable	Univariable Analysis		Multivariable Analysis[a]		Multivariable Analysis[b]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, yr	1.02 (1.01 to 1.03)	<0.01	1.01 (1.00 to 1.03)	0.06		
Males	1.19 (0.77 to 1.84)	0.44				
Lung involvement	1.19 (0.75 to 1.88)	0.47				
Double positivity	1.07 (0.64 to 1.78)	0.80				
Serum creatinine at presentation ≥5.7 mg/dl	4.83 (2.75 to 8.47)	<0.001	1.98 (0.96 to 4.10)	0.07		
Dialysis dependency at presentation	6.50 (3.68 to 11.47)	<0.001	[a]	[a]	3.2 (1.6 to 6.3)	0.001
Histopathologic classification		<0.01		0.15		
Focal (reference)						
Crescentic	20.29 (2.80 to 147.26)		8.38 (1.10 to 63.87)			
Mixed	11.67 (1.54 to 88.47)		6.77 (0.87 to 52.65)			
Sclerotic	25.72 (3.24 to 204.51)		11.17 (1.34 to 3.13)			
Percentage normal glomeruli	0.95 (0.93 to 0.98)	<0.001	0.97 (0.95 to 0.99)	<0.01	0.97 (0.95 to 0.99)	0.01
Percentage cellular crescents	1.02 (1.01 to 1.02)	<0.001	1.02 (1.00 to 1.05)	0.09		
Percentage globally Sclerotic glomeruli	1.01 (1.00 to 1.02)	0.20				
Interstitial fibrosis and tubular atrophy, score 2–3	1.88 (1.20 to 2.95)	<0.01	1.38 (0.87 to 2.18)	0.17		
Interstitial infiltrate, score 2–3	2.35 (1.44 to 3.83)	0.001	1.90 (1.16 to 3.13)	0.01	2.02 (1.2 to 3.5)	0.01
Tubulitis, present	1.51 (0.96 to 2.35)	0.07				

HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Each parameter that was significant in univariable analysis, was analyzed in a multivariable analysis including dialysis dependency at presentation. Dialysis dependency at presentation remained significant in each multivariable analysis with *P* values ≤0.002.
[b]Parameters that were significant in the multivariable analysis[a] were included in this multivariate analysis.

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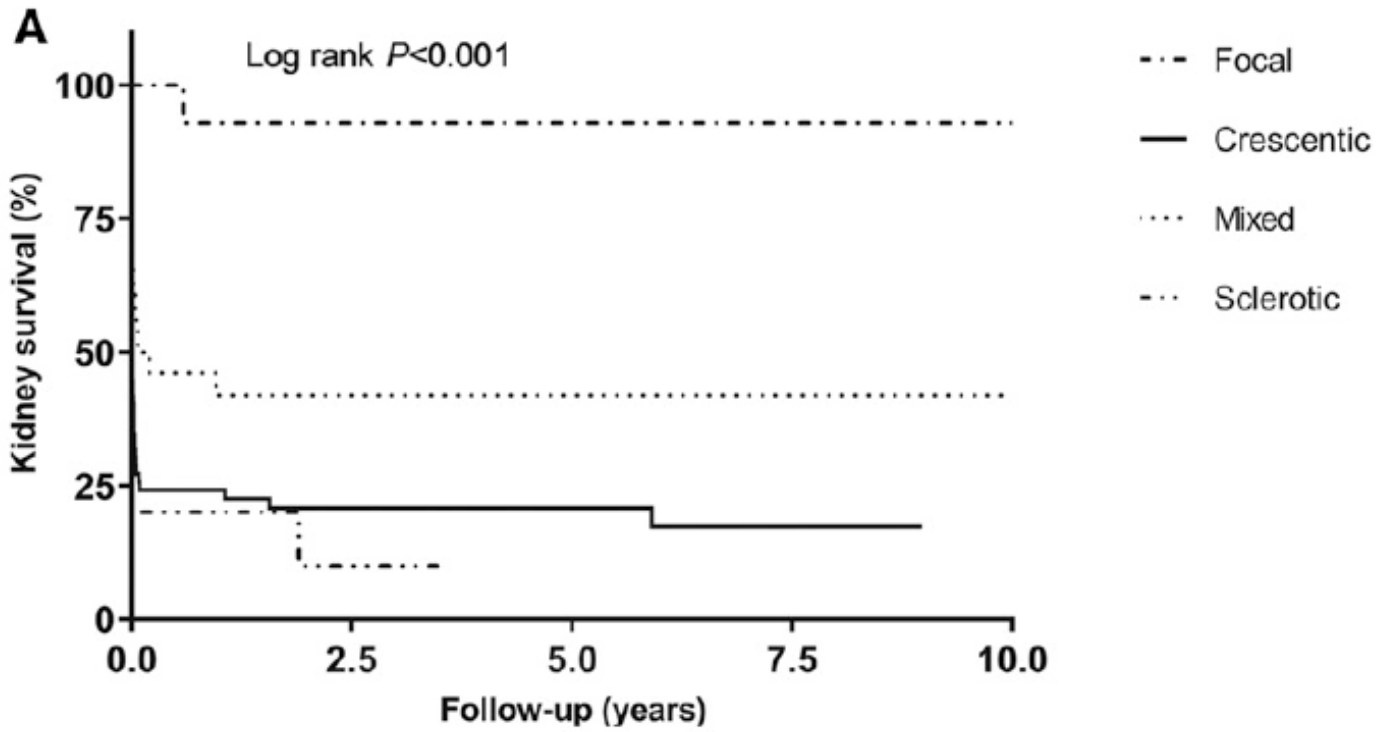
Survie rénale selon histologie



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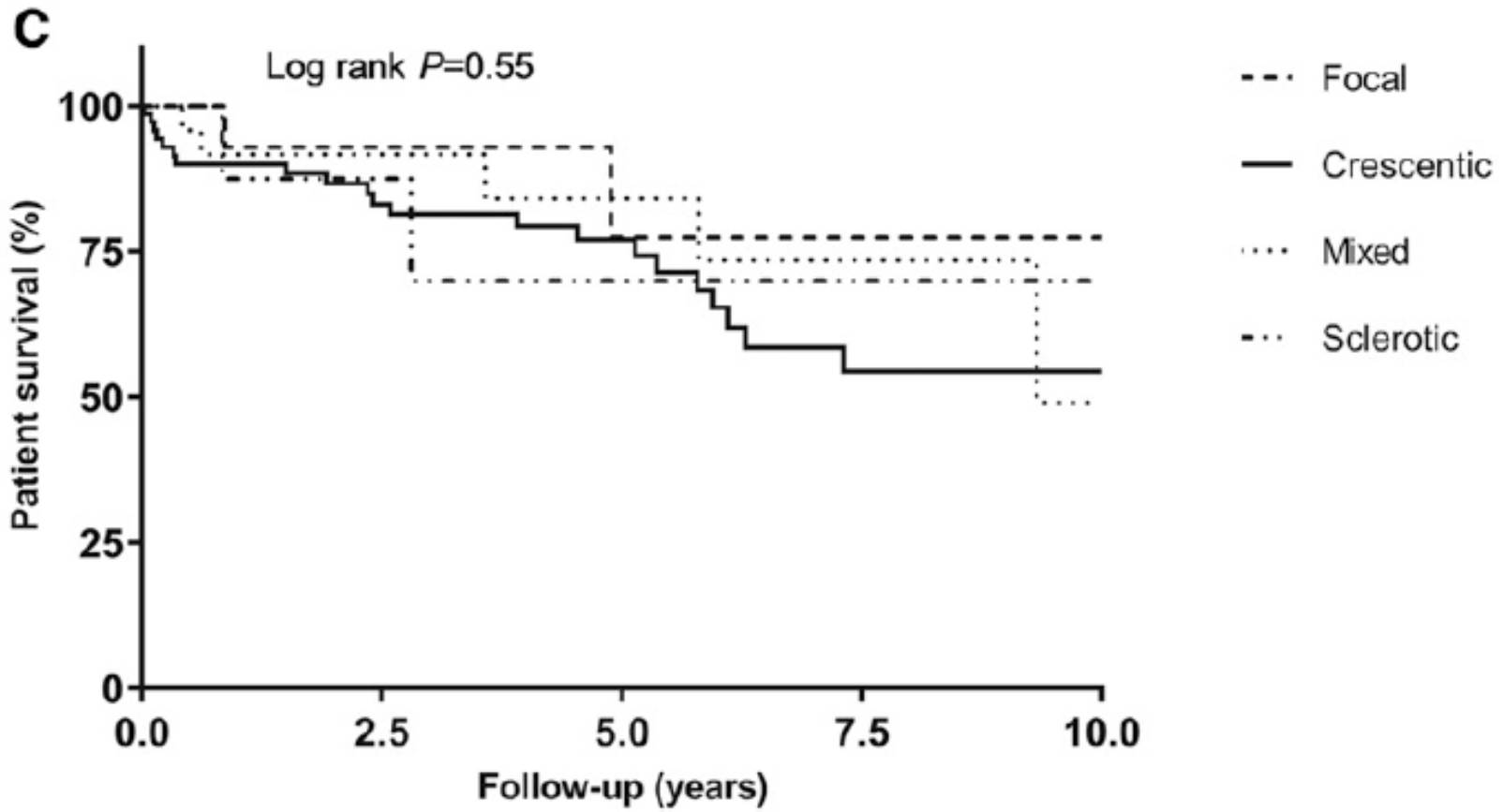
Survie patient selon histologie



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Récidive

- 2 à 14 %

- Délai
  - Médiane 4,3 ans (1 à 10 ans)

Survie après traitement de suppléance

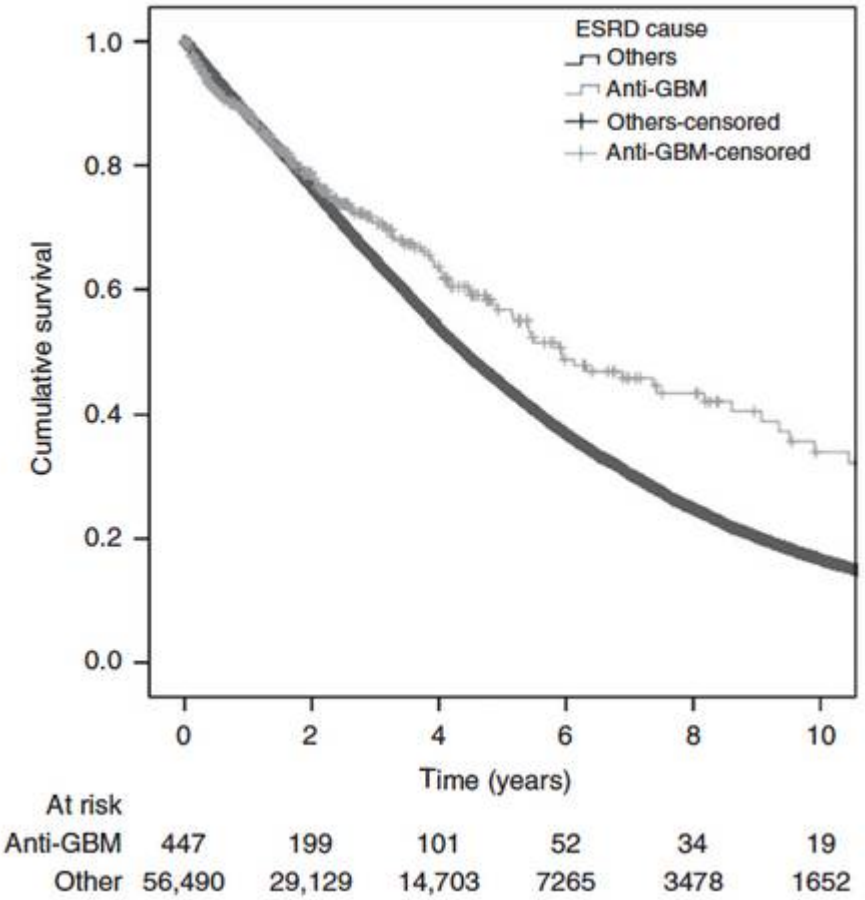
- Patients
  - ANZADATA : entre 1963 et 2010
  - 58422 avec RRT dont 449 pour antiGBM (0,7 %)

Tang W et al. Kid Int 2013;83:503-510.

Survie patient

- Décès:
  - 33 % (vs 46 %)
  - Médiane : 5,93 ans (vs 4,41)

- Facteurs de risque
  - Age
  - Hémorragie pulmonaire
  - Diabète



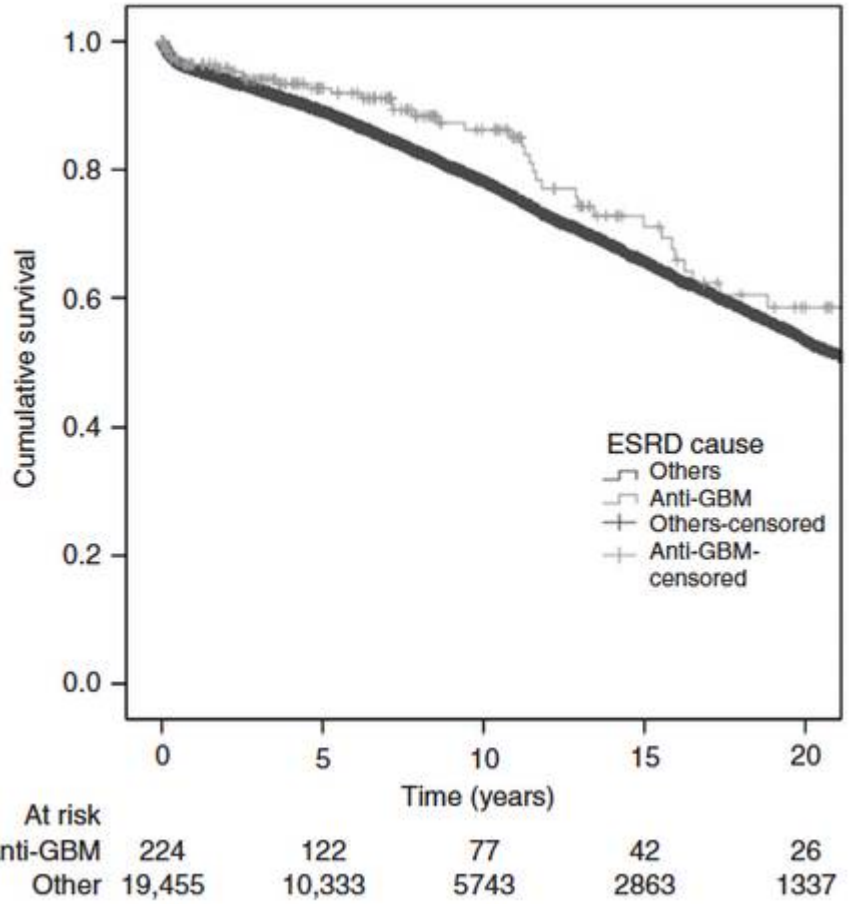
Tang W et al. Kid Int 2013;83:503-510.

Survie rénale (après dialyse)

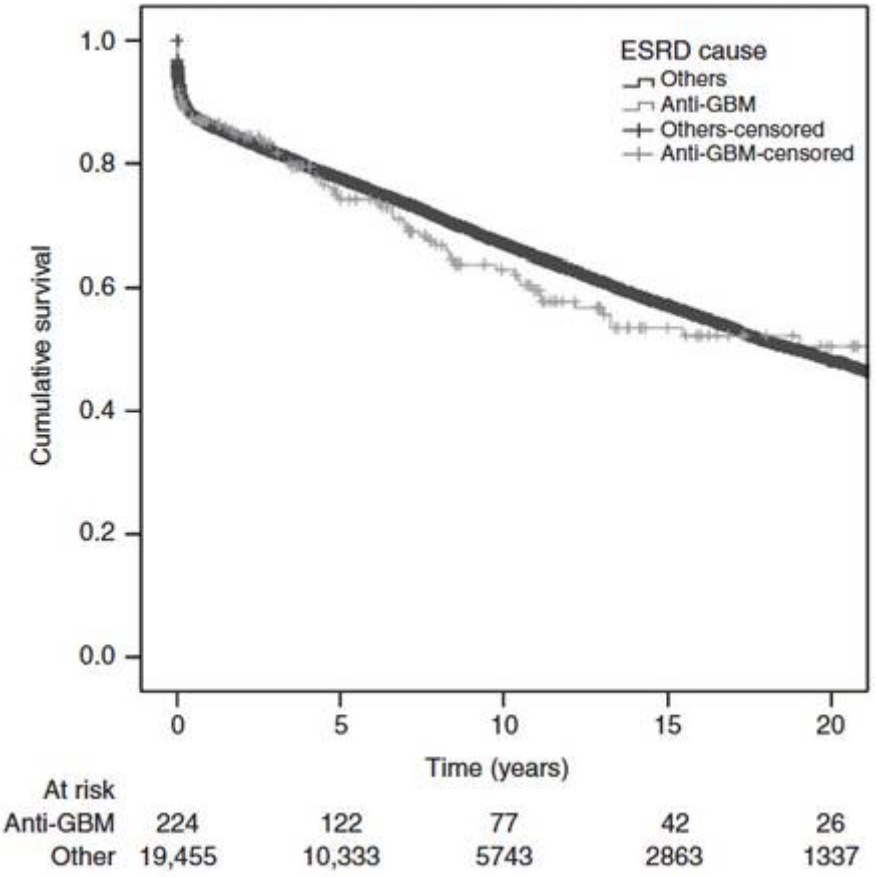
- Récupération d'une fonction rénale : 3 %

- Retour en dialyse : 77 %
  - Délai : [1.05 ans (0.1 – 7.92)].

Transplantation rénale



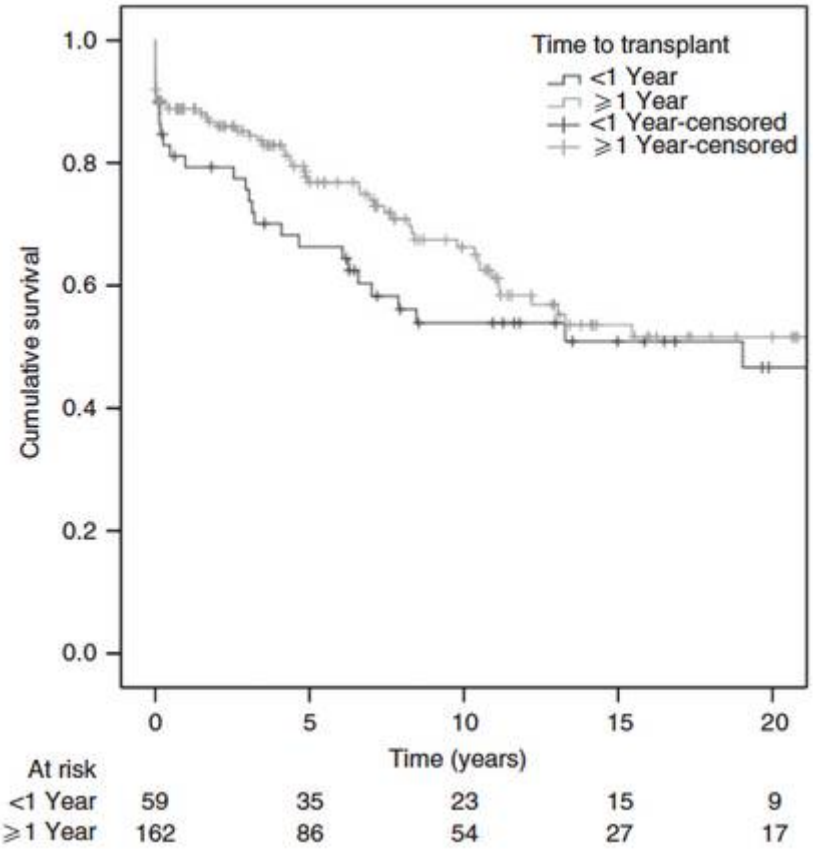
Patient



Greffon

Greffe rénale

- Délai avant transplantation
- Récidive
  - Entre 5 mois à 12 ans
  - 50 % si AcMBG présent
  - 5 à 15 % si plus de 6 mois après la disparition des Ac.
- Alport
  - AntiGBM : 5 % des cas
  - 15 % de dépôts sur MBG
  - 3 % de GNEC
  - 0,4 % de Maladie de Goodpasture
  - 75 % perte greffon



Formes particulières

- Association GEM

- AntiGBM atypique
  - Sans antiGBM associé
  - Rôle de dépôts monocloclaux d'Ig
  - Rôle de sous classe d'IgG (IgG4)

OhlssonS et al. Am J Kidney Dis 63: 289–293, 2014
Nasr SH, et al. Kidney Int 89: 897–908, 2016

Vascularite double positive

Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients

OPEN

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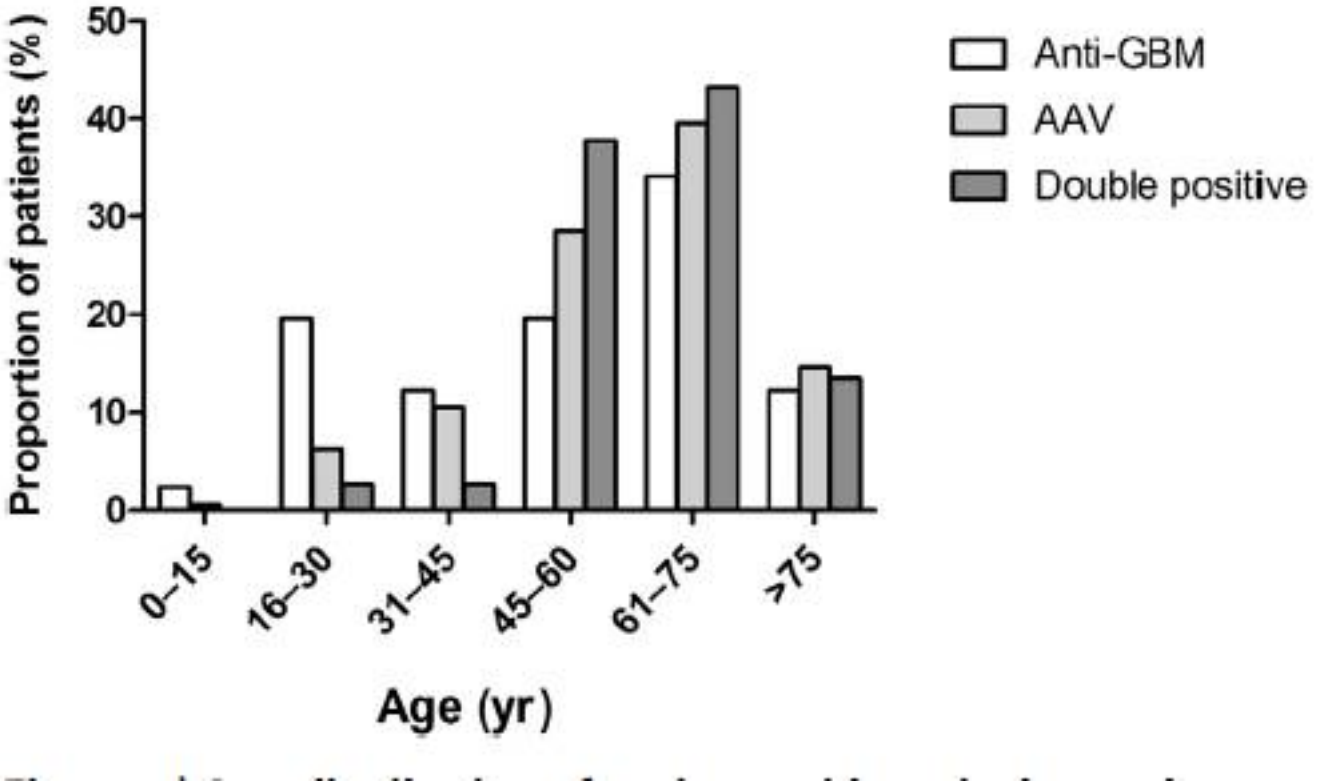
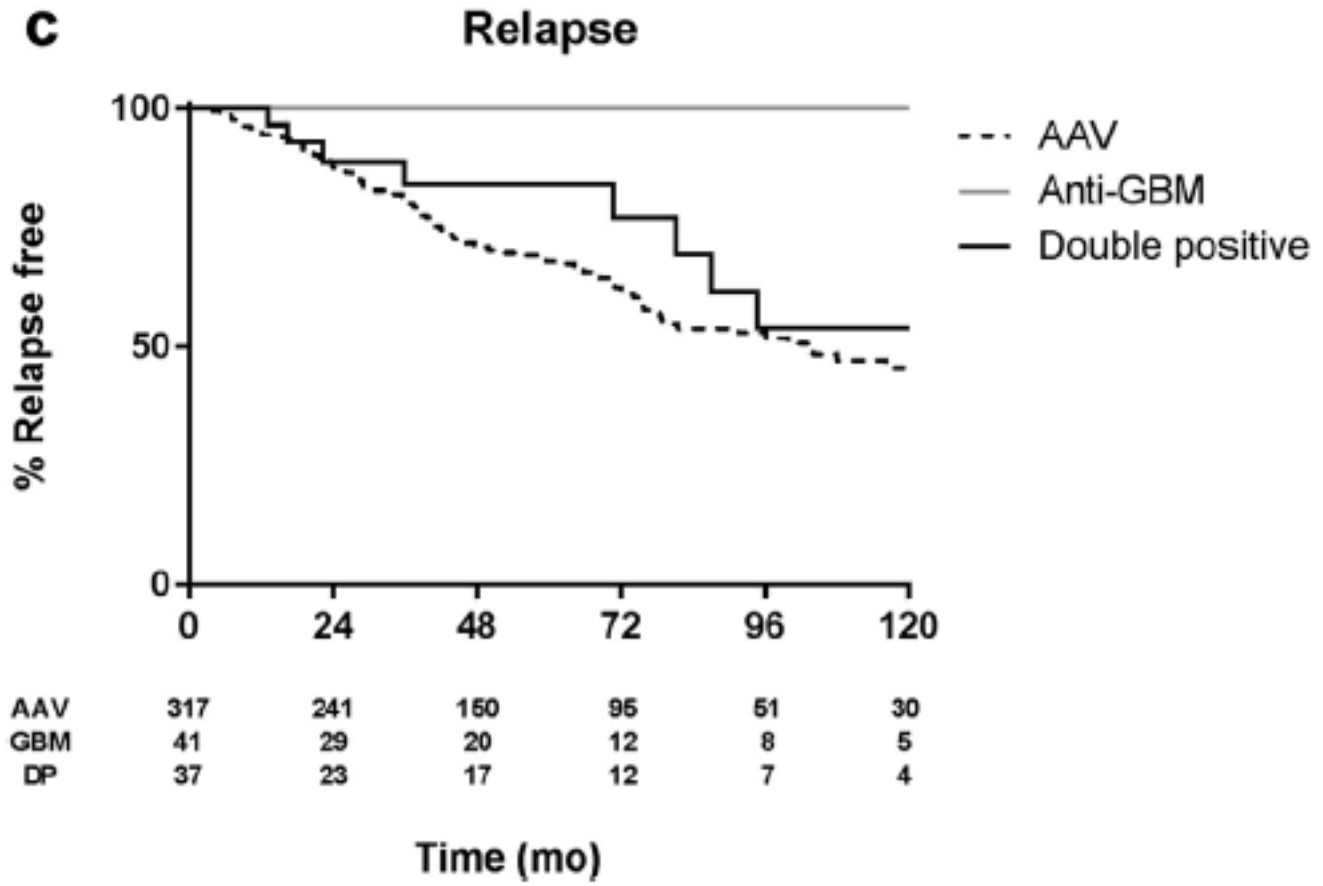
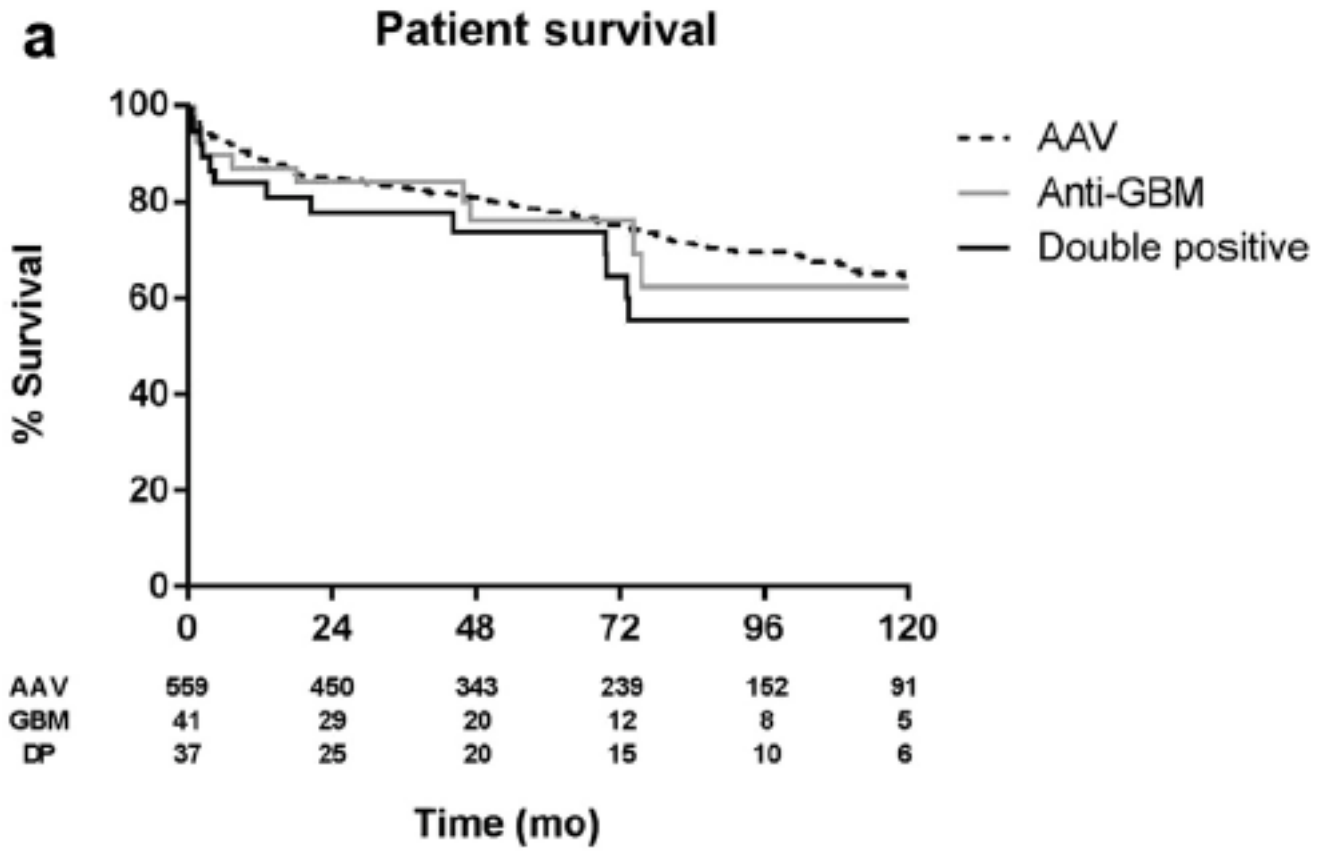
Vascularite double positive



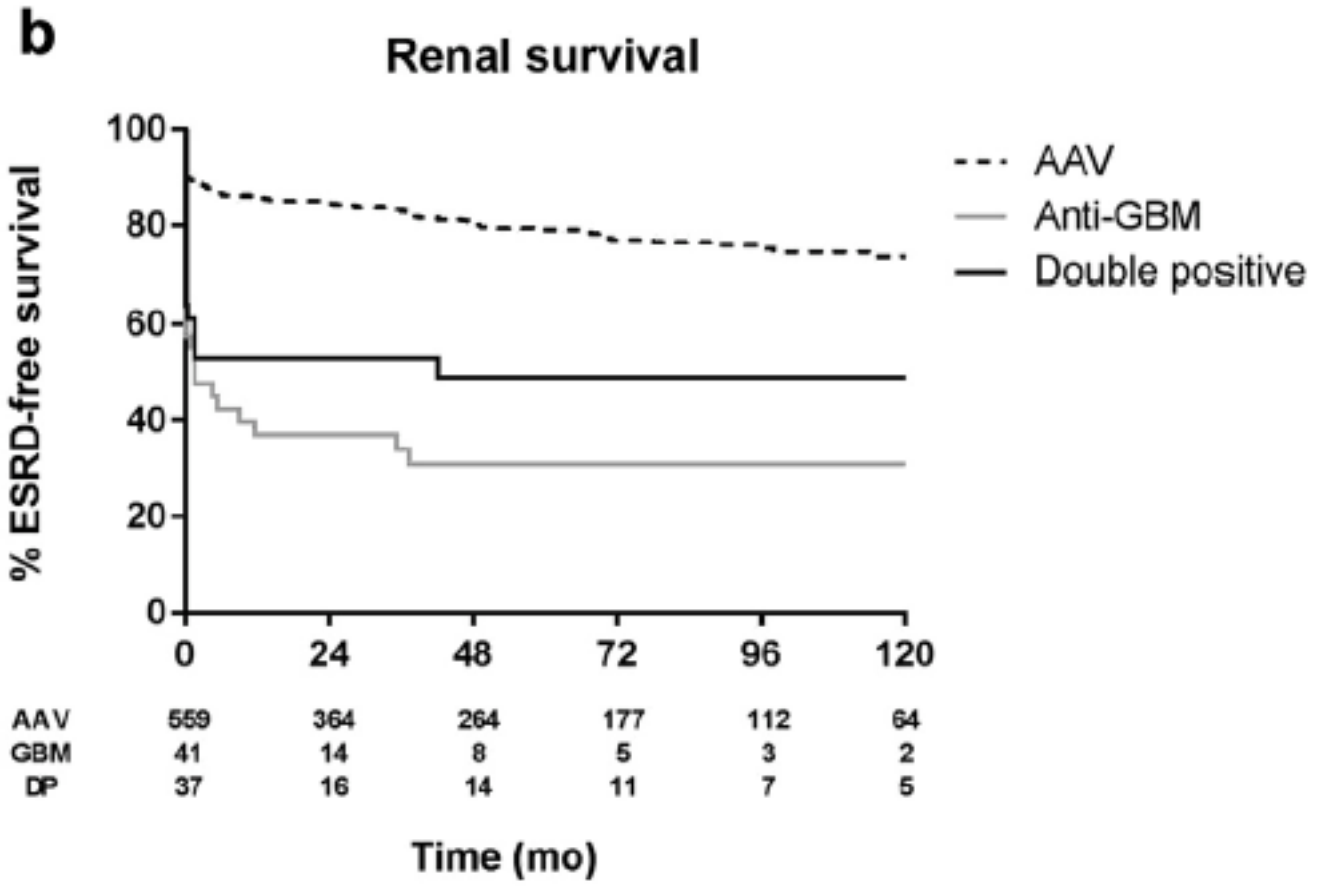
Vascularite double positive



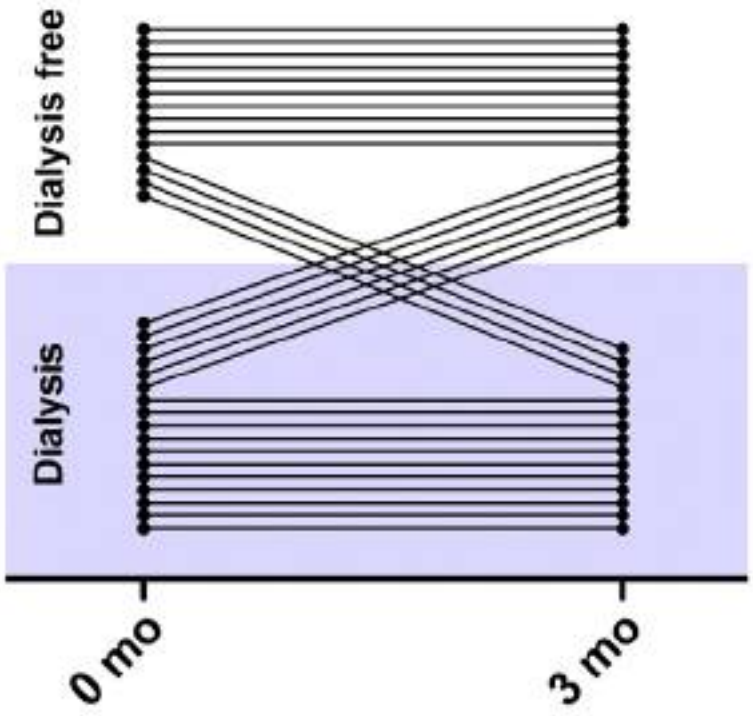
Vascularite double positive



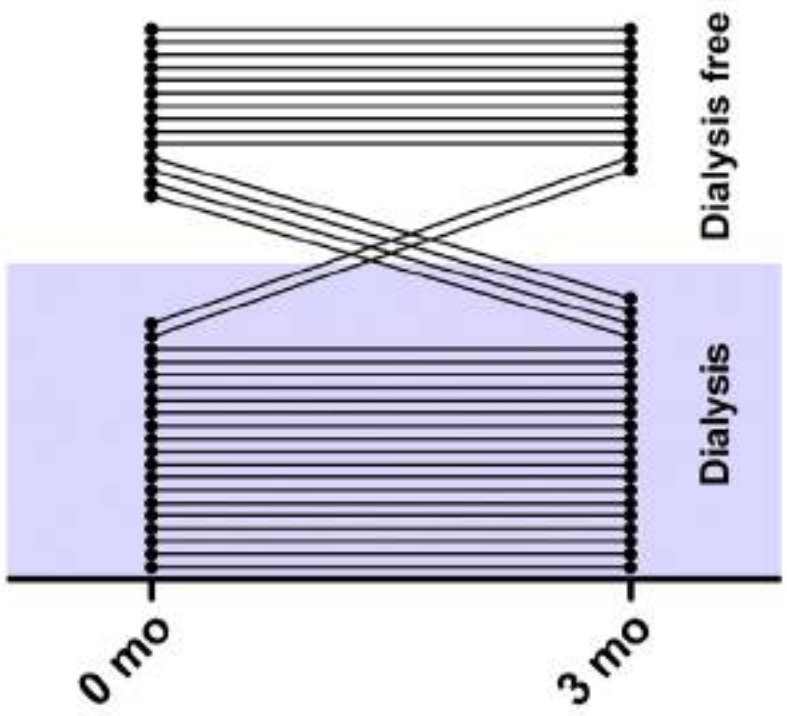
Vascularite double positive



Vascularite double positive



Double positive



Single positive

Vascularite double positive