Cancer-associated glomerulopathies

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Spectrum of renal involvement in cancer

- **Glomerulopathies**
- **Infiltration of renal parenchyma by malignant cells**
- **Retroperitoneal fibrosis**
- **Fluid and electrolyte disorders (tumor lysis syndrome, hypercalcemia, uric nephropathy, ectopic ADH secretion)**
- **Toxic nephropathies (chemotherapy, radiation nephritis)**

Outline

- **Epidemiology**

- **Carcinoma-associated glomerulopathies**
  - **Membranous nephropathy**
  - **Others : IgA/HSP, RPGN/vasculitis, AA-amyloidosis**

- **Hematologic malignancy-associated glomerulopathies**
  - **Hodgkin disease**
  - **CLL, related B-cell lymphomas, Waldenström macroglobulinemia**
  - **Plasma cell dyscrasias**
  - **Myeloproliferative neoplasms**

Epidemiology

- **Prevalence of proteinuria and hematuria in patients with cancer : 7 to 34% but overestimated :**
  - **threshold of proteinuria low;**
  - **hematuria detected by qualitative dipstick tests only.**

- **Prevalence of cancer in patients with glomerulopathy :**
  - **11% in pts with nephrotic syndrome (Lee, 1966);**
  - **risk for cancer x 3.5 at 1-4 years vs general population but not confirmed later (Danish Kidney Biopsy Registry : Birkeland, 2003);**
  - **risk x 8.3 and 5.4 for bladder and lung cancers in patients with alb. to creat. ratio in the highest quintile (Jørgensen, 2008).**

Potential detection bias

- **Patients with membranous nephropathy more aggressively screened for cancer**

- **Demographic characteristics of the population : the elderly (membranous nephropathy and cancer more frequent)**

- **Use of alkylating agents to treat glomerular disease**

Membranous nephropathy and cancer

- Association first reported in 1966 (Lee et al)
- Prevalence of cancer in pts with MN : 6% - 22%
- Most cases (80%) discovered before or at the time of kidney diagnosis
- Age- and sex- adjusted standardized incidence ratio : 2.25 ; continues to increase for more than 5 years after histologic diagnosis of nephropathy (Bjørneklett, 2007)
- Heavy smoking increases the likelyhood of malignancy in MN patients
- Most frequently associated tumors : lung, gastrointestinal, and prostate carcinomas

Criteria for the diagnosis of *paraneoplastic* glomerulopathy

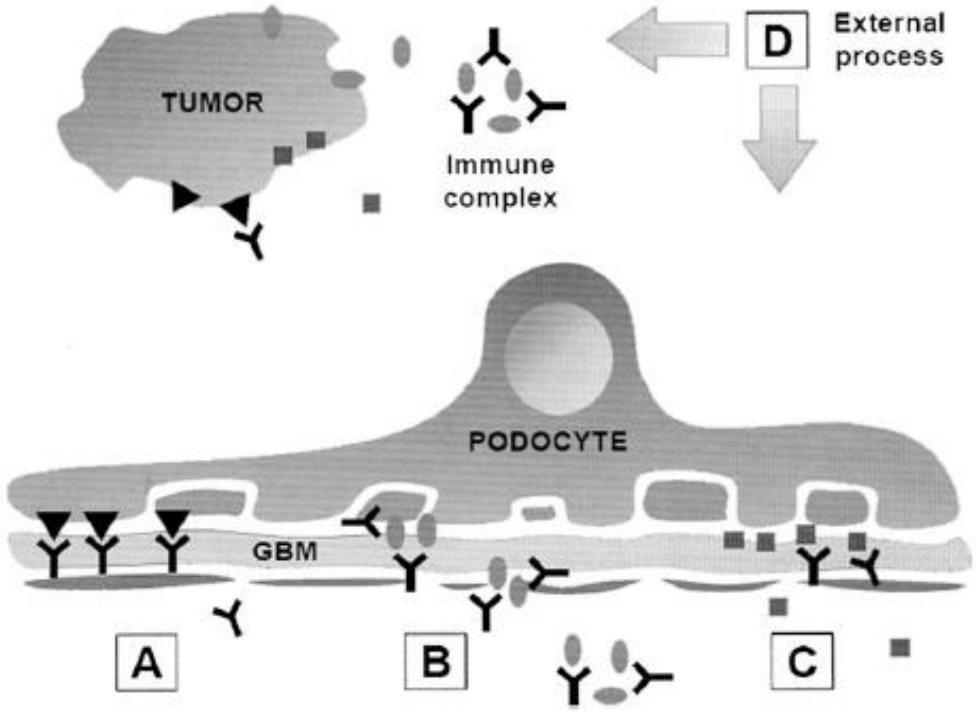
- **A remission** occurs after complete removal of the tumor by surgery, chemotherapy or other treatments

- **A renal relapse** accompanies recurrence of the neoplasia

- **A pathophysiologic link** is established between cancer and MN : detection of tumor antigens and antitumor antibodies within subepithelial immune deposits

☞ **However, these criteria are rarely fulfilled**

Mechanisms by which solid tumors and MN may be linked



A : Shared antigen/epitope on tumor and podocyte

B : Shed tumor antigen → blood immune complexes

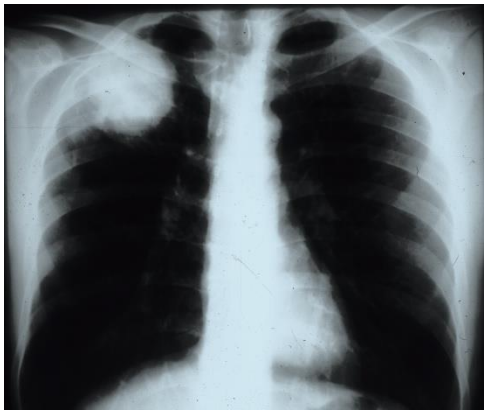
C : « Planted » tumor antigen →*in situ* immune complexes

D : Oncogenic virus or altered immune function

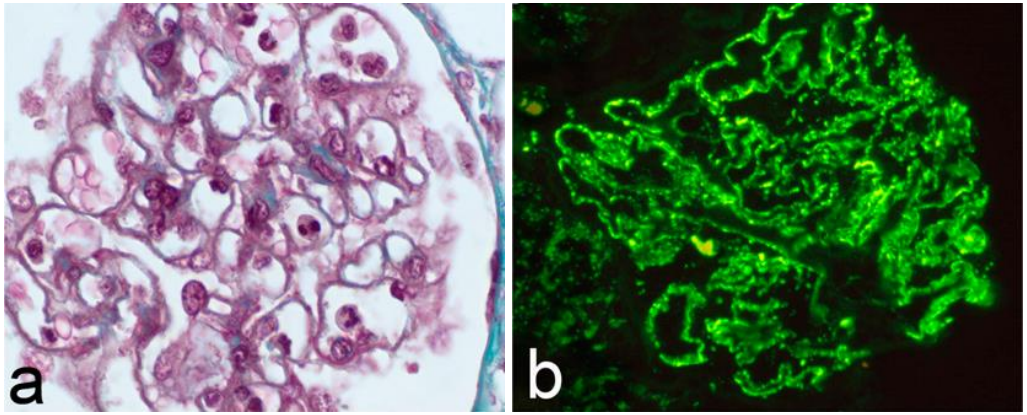
Beck et al, Seminars Nephrol 2010 30:635

A case of paraneoplastic glomerulopathy

- **Male, 49**
- **Heavy smoker (25 year packs)**
- **Anemia, weight loss**



Opacity in the right lung apex
Epidermoid lung cancer
Nephrotic syndrome (2 months later)



Membranous nephropathy

- Complete remission of kidney disease after 3 months following surgery (10-year follow-up)

Should all patients > 50 years be explored in search of cancer ?

- **Painful**
- **Costly**
- **Low yield**

☞ **Which patients should be targeted ?**

Recent advances in diagnostic tools

- **Determination of subclass of IgG deposited in glomeruli**

- **Assays of anti-PLA2R antibodies in blood and PLA2R antigen in kidney biopsy (immune deposits)**

- **Number of inflammatory cells/glomeruli**

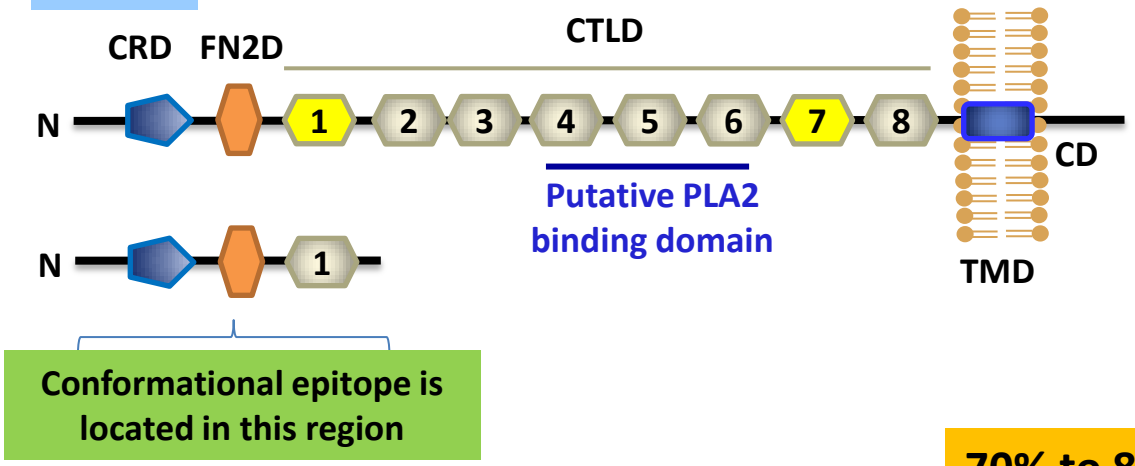
IgG subclass distribution according to underlying disease

	IgG_1	IgG_2	IgG_3	IgG_4
Idiopathic	**+ to +++**	**+**	**+**	**+++**
Lupus	**+++**	**+++**	**++**	±
Neoplasia	**+++**	**+++**	**+**	**0 to ++**

Noël LH et al, Clin Immunol Immunopathol 1988, 46:186 ; Ohtani et al, NDT, 2004, 19:574 ; Qu et al, NDT 2012, 27:1931 ; Debiec, personal data

A paradigm shift in diagnostic, monitoring and classification of patients with MN

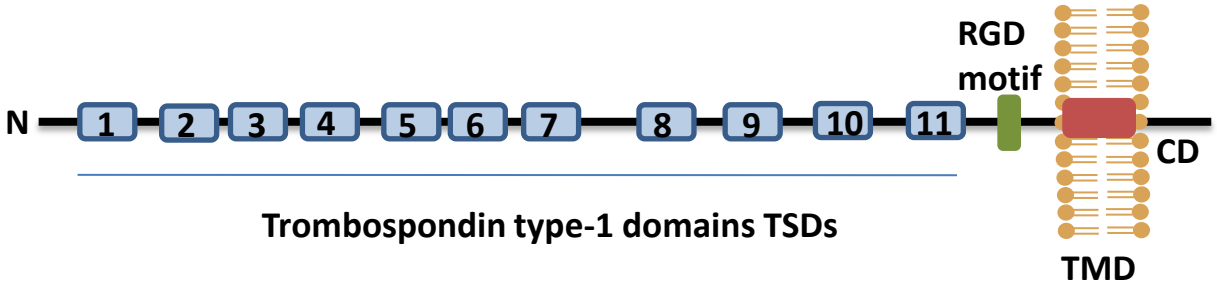
PLA2R



Beck et al, NEJM 2009,361:11
Kao et al, JASN 2015,26:291
Fresquet et al, JASN 2015,26:302
Seitz et al, JASN 2016, 27:1517;
JASN 2018 ;29:401
(epitope speading correlated with outcome)

70% to 85% of adult MN patients

Thrombospondin type-1 domain containing 7A (THSD7A)

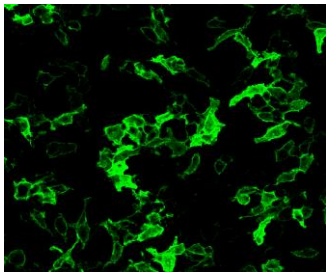


Tomas et al,
NEJM 2014, 371: 2277
Tomas et al,
J Clin Invest 2016, 126:2519

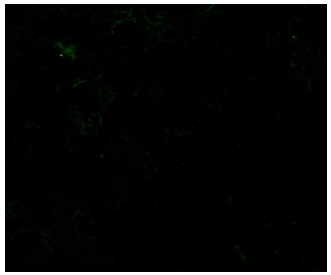
10 % of PLA2R-negative patients with MN

Serological tests for the diagnosis and monitoring of patients with MN

→ **Indirect immunofluorescence for PLA2R and THSD7A** →

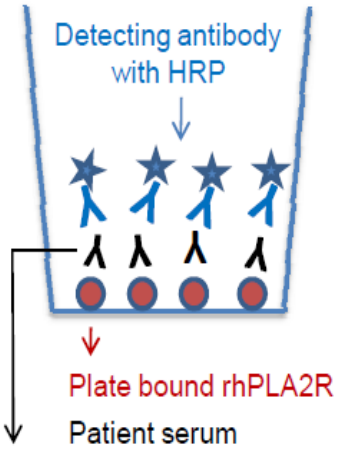


HEK293 cells transfected with cDNA for PLA2R



HEK293 cells non transfected

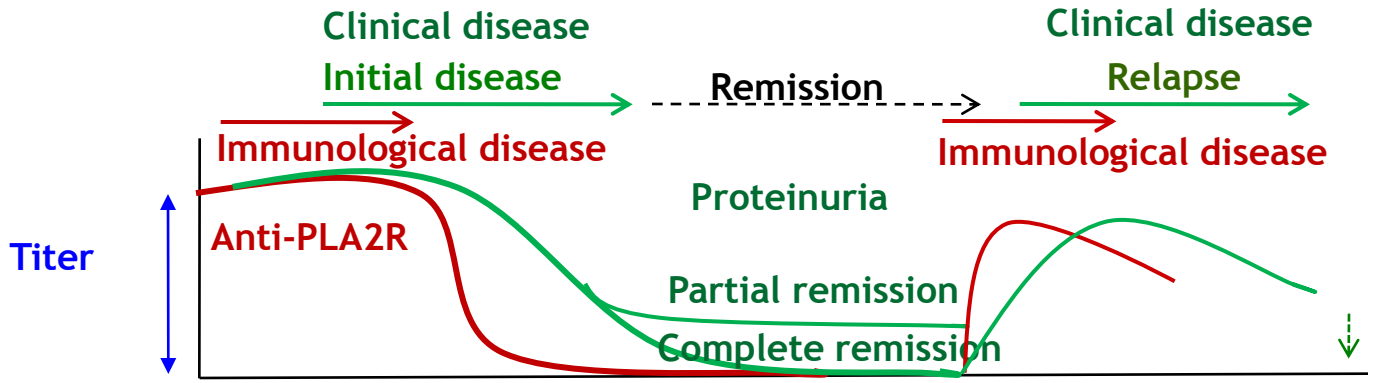
ELISA-PLA2R



Meta-analysis (2014)

- 15 studies, 2212 patients
- **Specificity = 99%**
  (95% CI : 96-100%)
- **Sensitivity = 78%**
  (95% CI :66-87%)

Du et al, PLoSOne 2014, 9:e104936



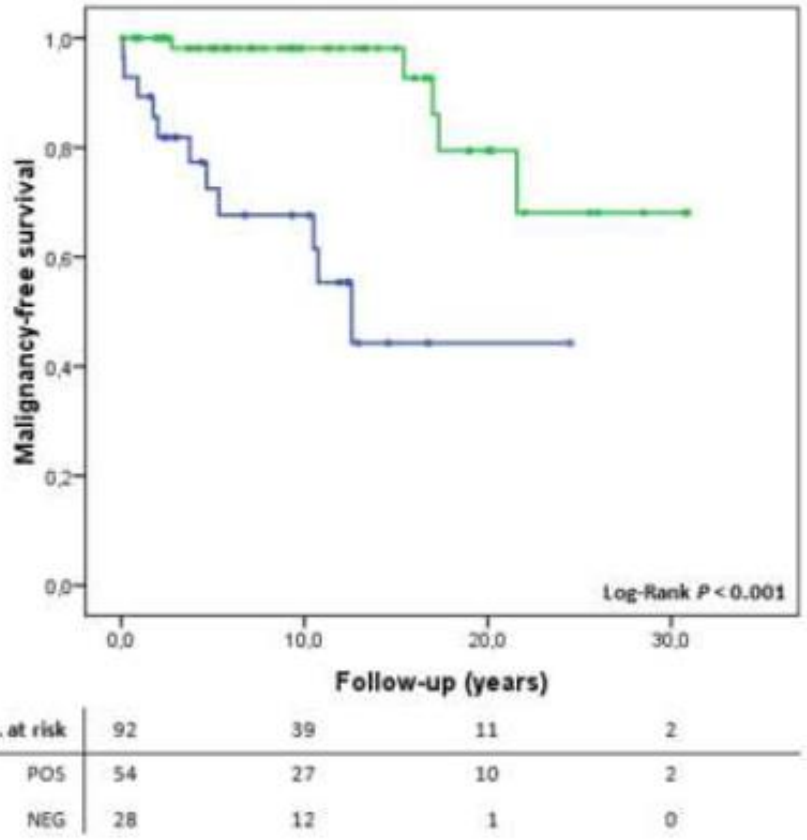
The association of malignancy with MN is stronger if anti-PLA_2R serology is negative

Table 4. Multiple Cox regression analysis for patients malignancy-free survival in iMN.

Parameter	Hazard ratio	95% CI	*P*
Positive aPLA2R*	0.078	0.017 – 0.360	0.001
Age*	1.058	1.009 – 1.109	0.02
Male gender	5.274	1.342 – 20.727	0.02
Proteinuria†	1.201	1.064 – 1.356	0.003
Immunosuppression†	0.668	0.121 – 3.681	0.64

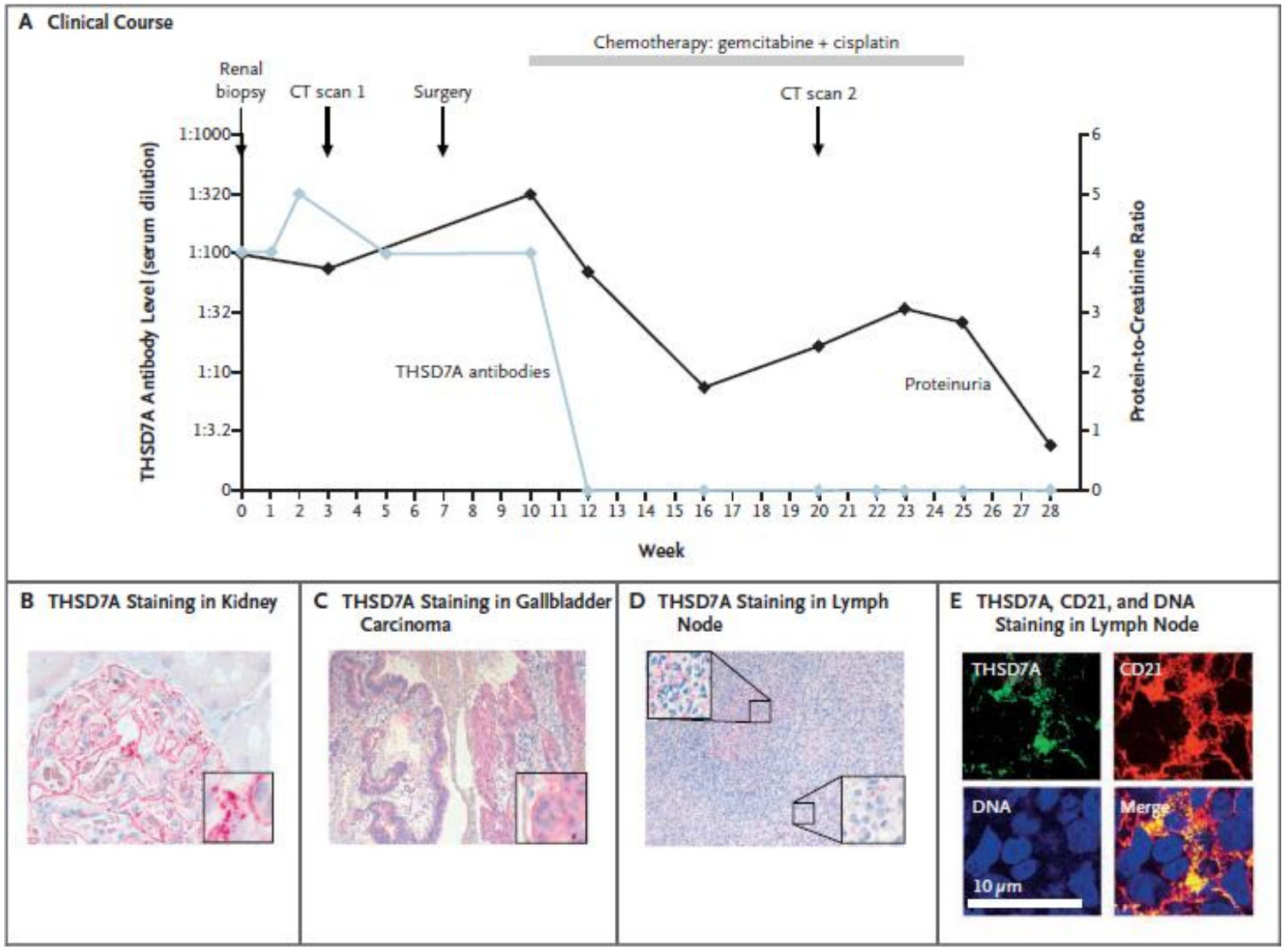
CI, confidence interval.

* At the time of renal biopsy.



Timmermans S, et al. Am J Kidney Dis 2013 62:1223

A role for THSD7A in cancer-associated membranous nephropathy



Hoxha et al, NEJM 2016 374:1995

Prevalence of PLA2R and THSD7A-Ab in cancer patients is controversial

Hamburg/Boston series

Eight/40 patients with THSD7A-associated MN developed a malignancy within 3 months

International series

Eight/49 patients with THSD7A-associated MN, but only 3 within 2 years

Chinese series

44 K-associated MN

- 1 THSD7A-Ab + (2%)

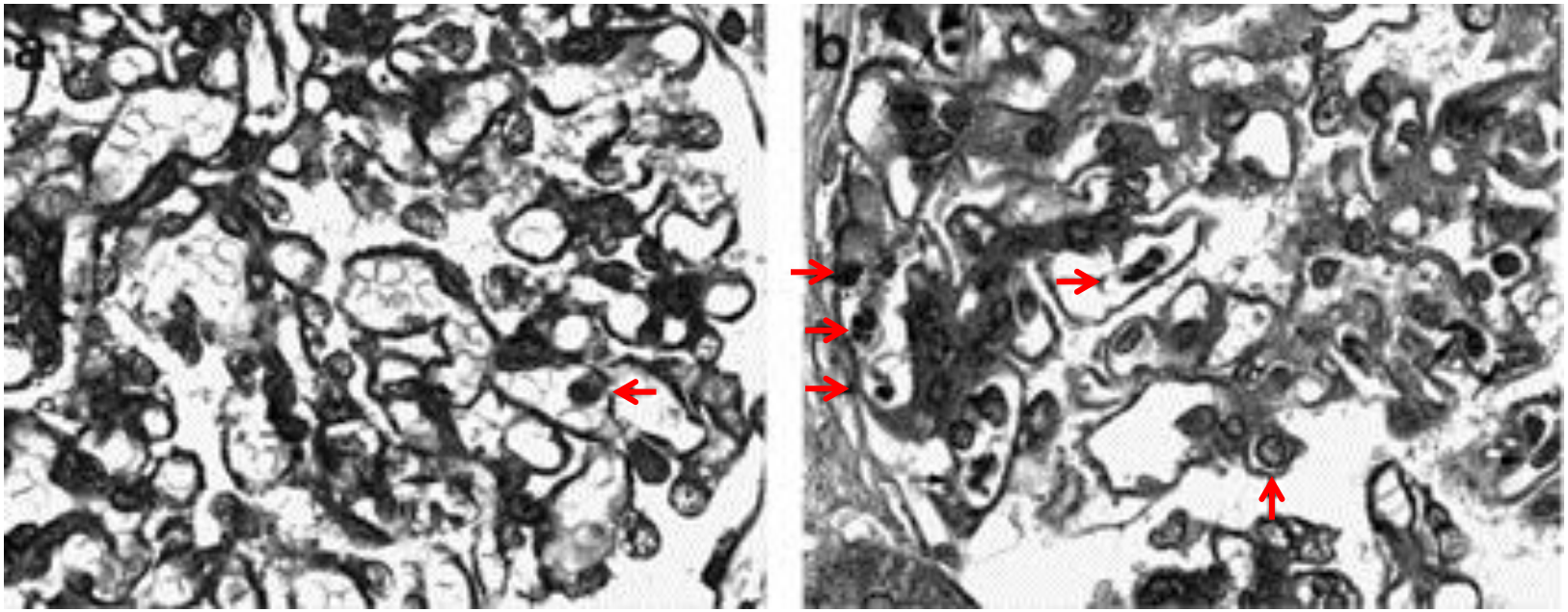
Urinary blader cancer > 7 years before MN

- 18 PLA2R-Ab + (41%)

Time interval < 6 months in 10/18 patients

Wang, Cui, …, Ronco, Zhao, Clin J Am Soc Nephrol. 2017; 12:164 ;
Hoxha et al, JASN 2017, 28:520; Zaghrini et al, Kidney Int. 2019; 95:666

Presence of inflammatory cells in glomeruli in cancer-related MN



Primary MN

K-related MN

Sensitivity = 92% and specificity = 75%
for a threshold of > 8 inflammatory cells/glomeruli

Lefaucheur, Kidney Int 2006, 70:1510

ASSOCIATED GLOMERULAR LESIONS WITH CANCERS

Membranous Nephropathy	Minimal change disease focal segmental glomerulosclerosis	IgA Nephropathy IgA Vasculitis	ANCA+/ANCA- crescentic glomerulonephritis
Carcinoma : Lung/bronchus GI/Prostate/Renal, Bladder, Breast Melanoma Thymoma (Hematologic malignancy)	Hoddgkin's disease Thymoma Renal/GI carcinoma	Renal/Lung /URT carcinoma Hematologic malignancy	Renal/Lung/URT carcinoma Thymoma
			MPGN: Renal/Lung/GI carcinoma

SEROLOGY

TSHD7A + PLA2R -/TSHD7A -	PLA2R +

SCREENING FOR OCCULT MALIGNANCY
Normal routing/targeted screening

ROUTINE SCREENING
All patients

- Patient/family clinical record
- Careful physical examination
- Laboratory testing
- Kidney and urinary tract US
- Standard age-specific screening for cancer (gynecological examination, PAP test, mammography, fecal occult blood test)

TARGETED SCREENING
According to patient's risk factors for cancer

Age > 60 years Thrombotic event	• Search for urine malignant cells +/- cystoscopy • PSA test • Abdominal US
Smoking	• Chest computed tomography • Upper respiratory tract examination +/- fibroscopy • Search for urine malignant cells +/- cystoscopy
Alcohol abuse	• Upper respiratory tract examination +/- fibroscopy • Liver US, gastroscopy, serum alpha-foetoprotein
Chronic hepatitis B and C	• Liver US , serum alpha-foetoprotein
Exposure to cyclophosphamide Doses > 36gr	• Search for urine malignant cells +/- cystoscopy

If malignancy not detected,
the patient should be carefully followed
because of long-term risk for K occurrence

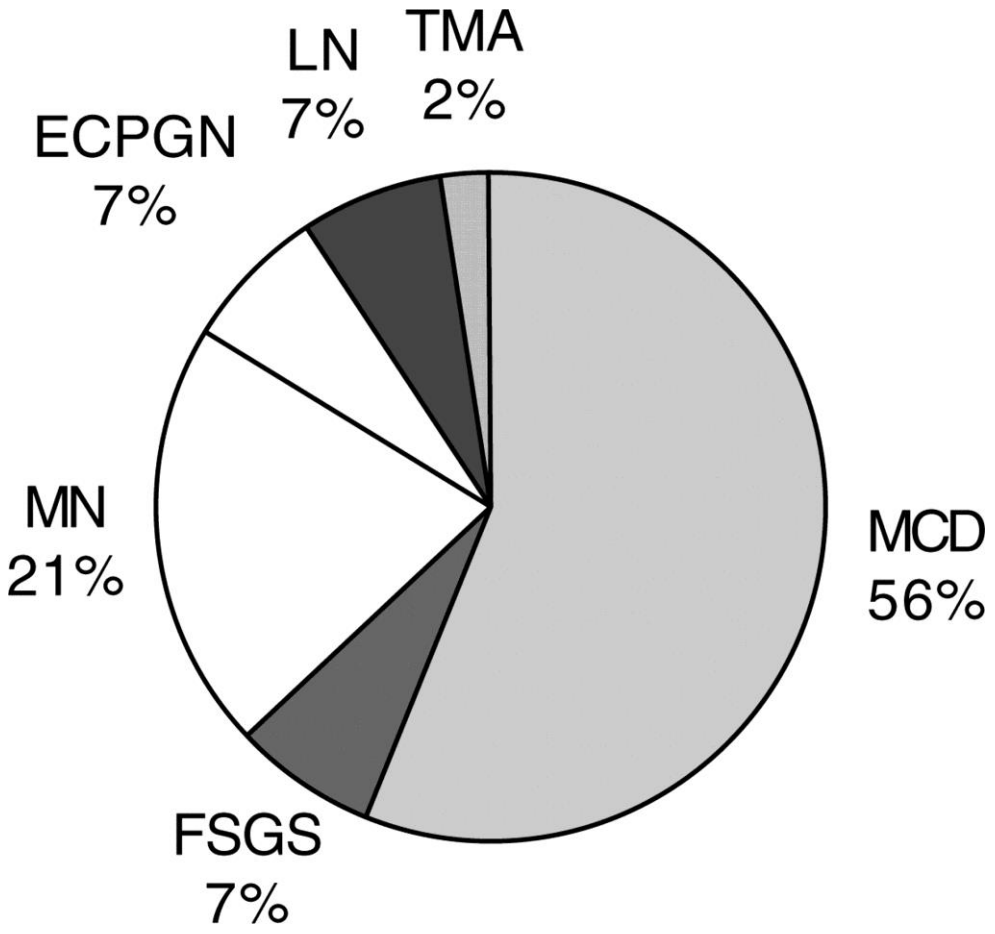
Other carcinoma-associated glomerulopathies

- **IgA nephropathy > 60 years : search for solid tumor in the respiratory tract, the buccal cavity and the nasopharynx**

- **Necrotic Henoch-Schönlein purpura (HSP) : search for cancer of the lung, upper respiratory and digestive tracts (Pillebout, 2002)**

- **ANCA-associated vasculitis : relative risk x 6 (Pankhurst, 2004)**

Thymoma-associated glomerulopathies (n = 40)



- **Rat Buffalo/Mna**
- **Th2 polarization**
- **Role of Treg**

Associated with lymphocyte-predominant thymoma

Karras et al, NDT 2005, 20:1075

Outline

- Epidemiology

- Carcinoma-associated glomerulopathies
  - Membranous nephropathy
  - Others : IgA, RPGN/vasculitis, AA-amyloidosis

- Hematologic malignancy-associated glomerulopathies
  - Hodgkin disease
  - CLL, related B-cell lymphomas, Waldenström macroglubulinemia
  - Plasma cell dyscrasias
  - Myeloproliferative neoplasms

Hematologic malignancy-associated glomerulopathies

- **Clinical link usually more obvious**

- **Outcome of kidney involvement parallels that of hematologic malignancy**

- **Pathophysiological link more easily established, mostly a secreted immunoglobulin or a fragment thereof**

Glomerulopathy in Hodgkin lymphoma

- Prevalence in 1700 patients (Plager 1977 ; Kramer, 1981)
  - minimal change disease (MCD) : 0.4 %
  - AA-amyloidosis : 0.1%

- At present, MCD is the prevailing manifestation :
  - revealing the lymphoma in ~ 40% of cases
  - displaying a high frequency of steroid resistance (50%) and ciclosporine resistance (36%)
  - remission induced by effective treatment of Hodgkin lymphoma (even without corticosteroids)
  - usually relapses simultaneously with hematologic malignancy

- MCD seems more frequent with mixed cellularity and nodular sclerosis subtype

Glomerulopathy in Chronic Lymphocytic Leukemia (CLL)

- First association with nephrotic syndrome reported in 1957 (Scott)
- Prevalence of nephrotic syndrome 1% -2%
- Usually fulfills the 3 criteria of a paraneoplastic syndrome
- Cryoglobulin or non cryoprecipitating M-component in ~ 50% of patients (only 5%-10% in those without renal involvement)

- Three major types of glomerulopathy :
  - cryoglobulin-related MPGN (type I or type II)
  - immunotactoid glomerulopathy (atypical MN or MPGN)
  - MIDD

Patient with CLL and acute nephritic syndrome

- 50-years old Caucasian female
- Diagnosis of CLL
- + 3 Years : detection of circulating IgGk
- + 6 Months : Acute nephritic syndrome

  S. Creat, 2.8 mg/dL

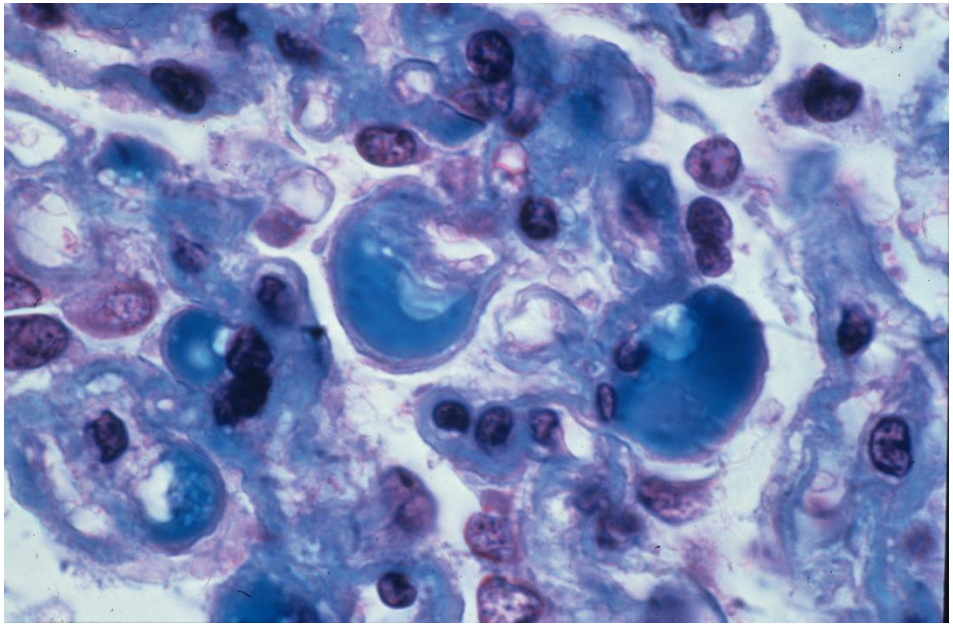
  Proteinuria, 7 g/day, macroscopic hematuria

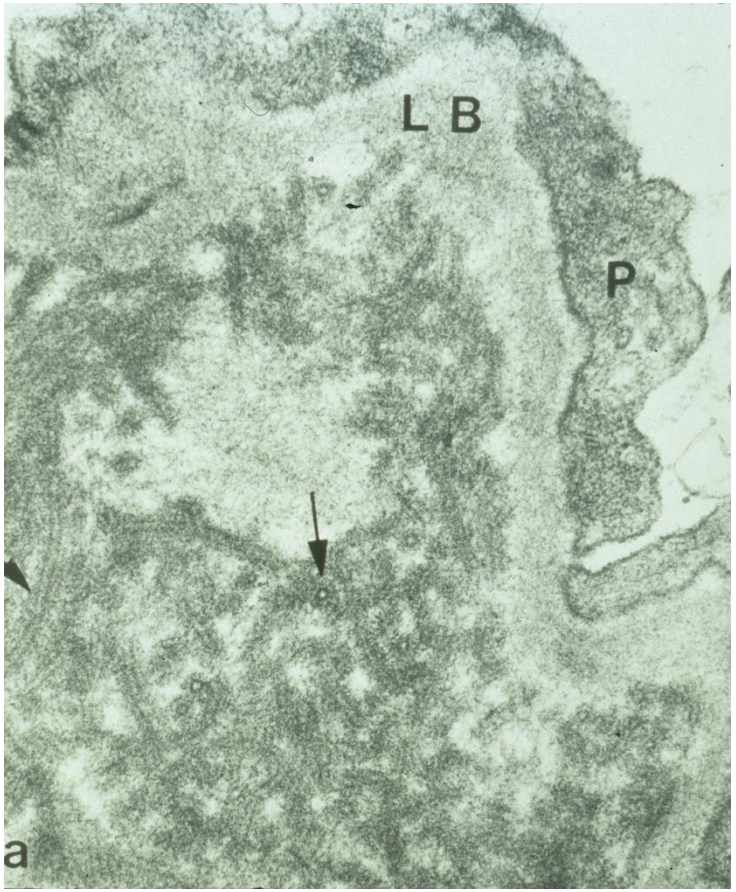
  Type I cryo = IgGk, complement (C') hemolytic activity not detectable

☞ Kidney biopsy : MPGN with thrombi, IgG, K, C1q, C3

Patient with CLL and type-I cryo

MPGN: thrombi with IgG, K, C1q and C3





☞ **After chemotherapy**

- S. Creat, 1 mg/dL
- Proteinuria, 1 g/day, RBC < 1000/mL
- Cryo IgGk (0.05 g/L), C' hemolytic activity restored

Patient with CLL and the nephrotic syndrome

- 59-year old Caucasian male

- 4 years : CLL + nephrotic syndrome (proteinuria = 8 g/day) with hypertension, microscopic hematuria, mild renal failure (sCreat = 1.4 mg/dL)

↳ No kidney biopsy (platelet count = $36x10^6$/ml)

↳ Chemotherapy : CHOP for 18 months followed by chlorambucil for 12 months

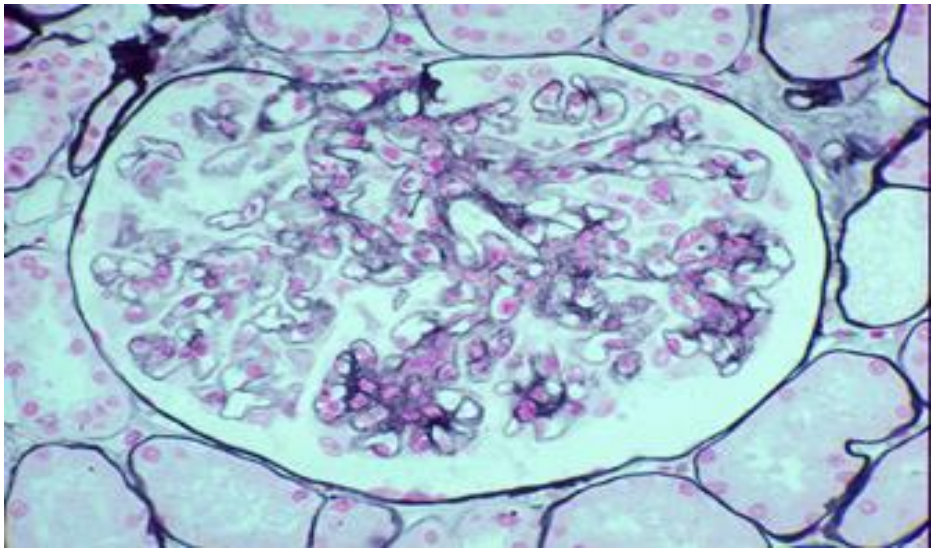
- At the end of chemotherapy :
  - proteinuria : 2 to 3 g/day ; serum albumin : 35 g/L ; sCreat : 80 µmol/L
  - white blood cell count : $4x10^6$/ml (31% lymphocytes)
  - platelet cell count : $110x10^6$/ml

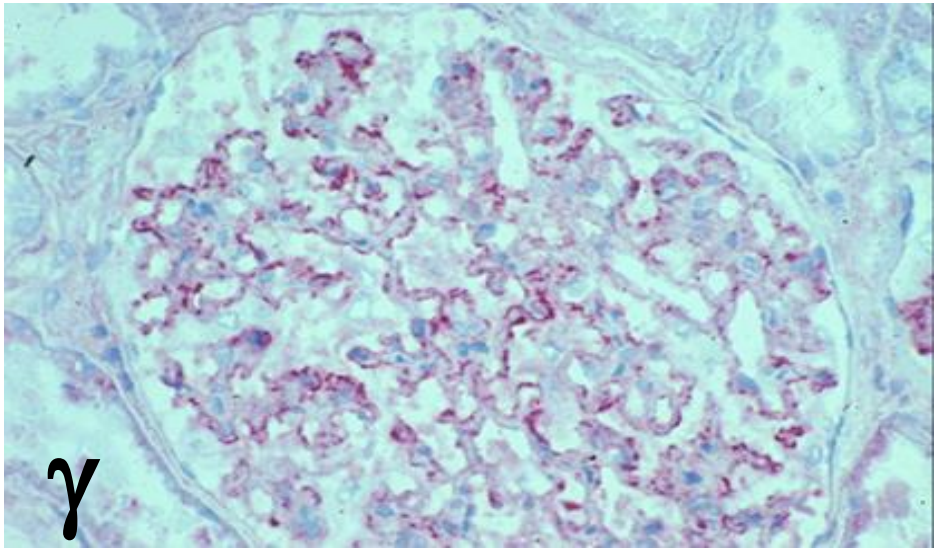
↳ Kidney biopsy

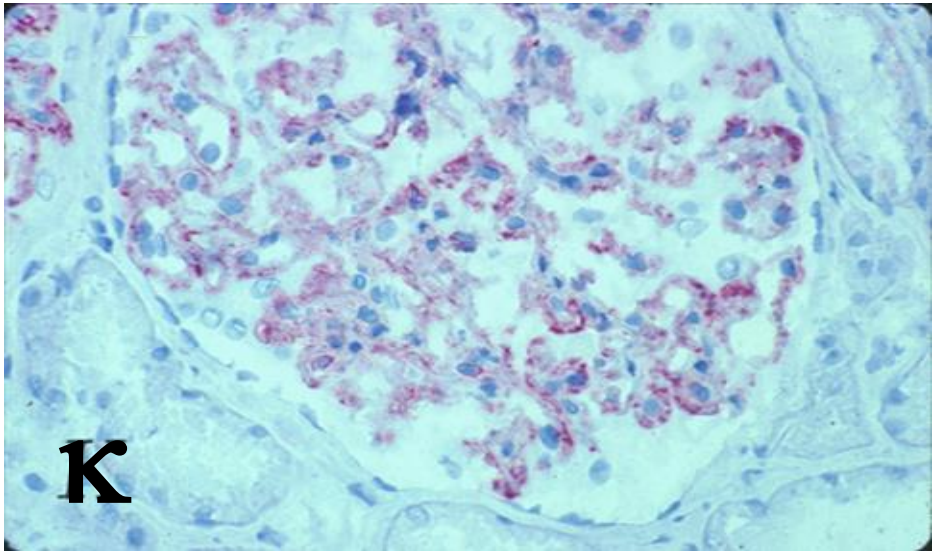
Patient with CLL and the nephrotic syndrome : Immunological data

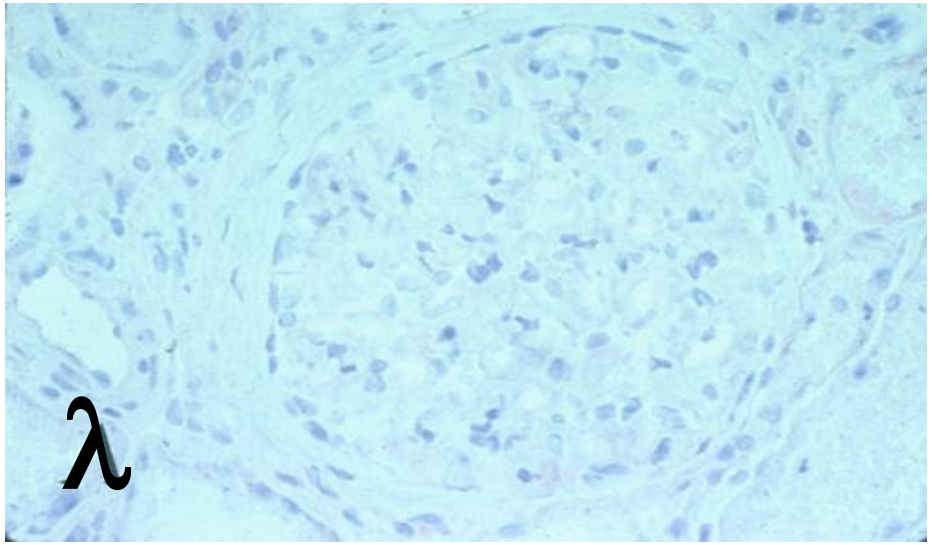
- γ-globulin = 4 g/L
- No M-component in serum and urine (immunofixation)
- No cryoglobulin
- Complement consumption (CH_{50} = 33%)
- Cytoplasmic spots in a few blood cells stained with anti-g and anti-k chain antibodies

Patient with CLL and the nephrotic syndrome







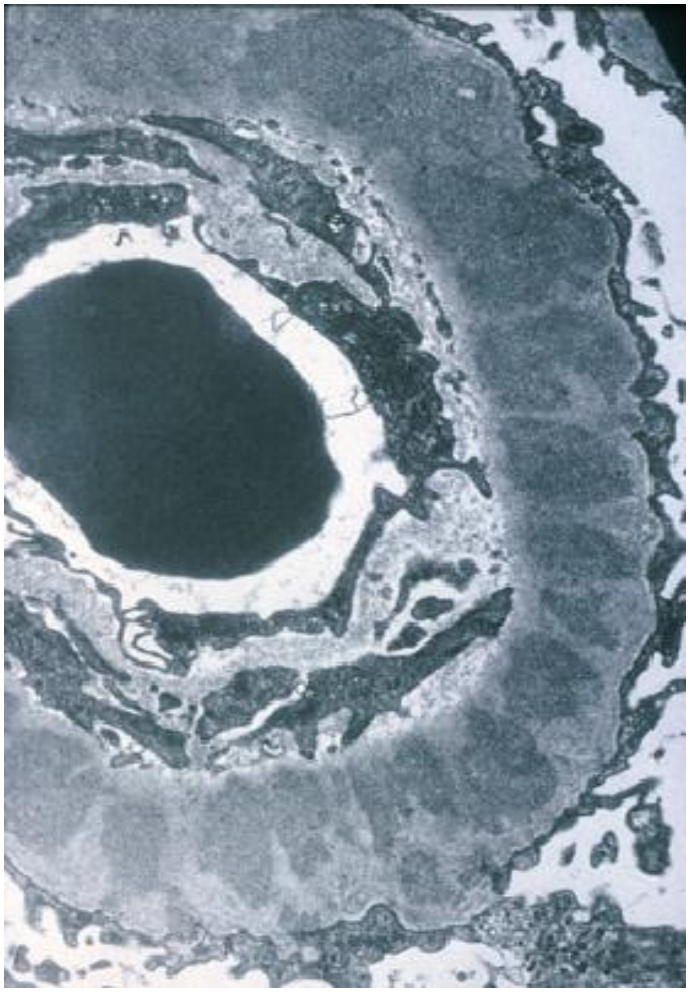


Glomerulonephritis with monotypic γκ deposits

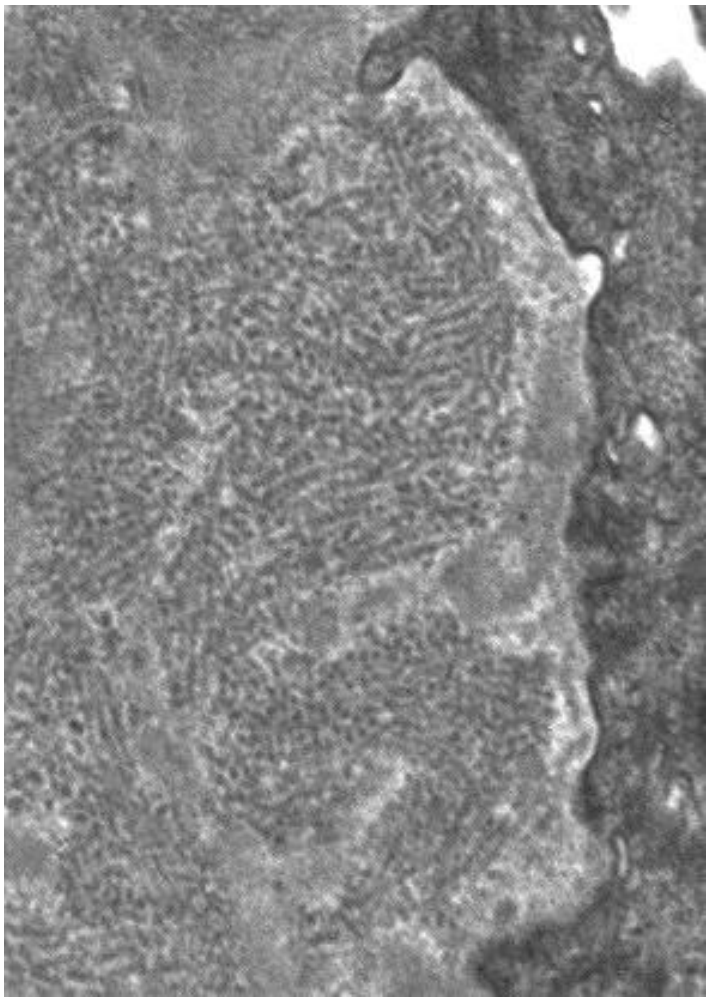
- **Amyloidosis (Congo red negative) excluded**
- **Cryoglobulinemia (type 1) excluded**
- **Immune-complex like proliferative GN with monoclonal IgG deposits (*Nasr et al, Kidney Int, 2004, 65:85*)**
- **Membranous-like glomerulopathy with (not always) masked IgG kappa deposits (MGMID)**
- **Immunotactoid GN ?**

→ Electron microscopy

Patient with CLL and the nephrotic syndrome



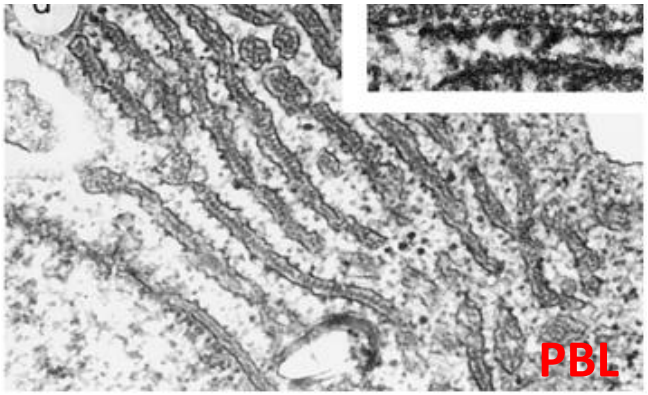
X 4, 400



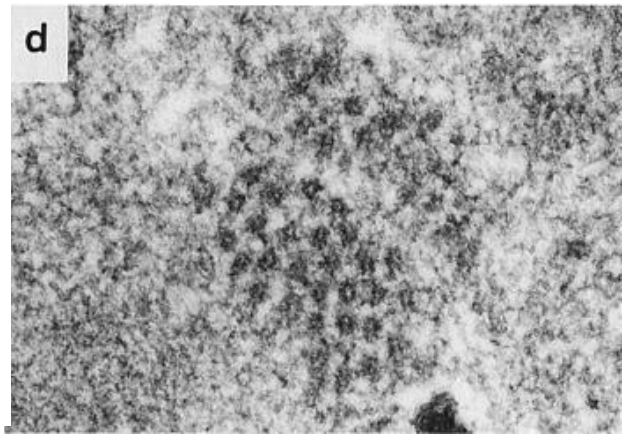
X 20, 000

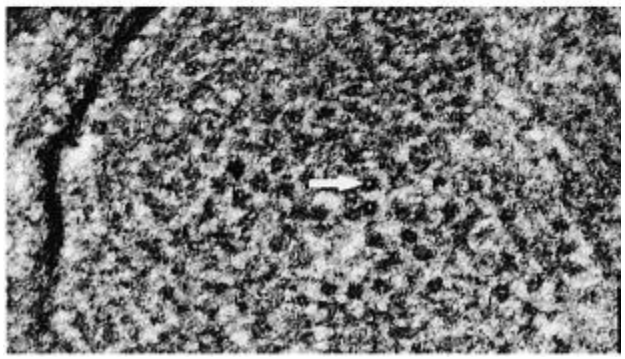
Pathogenesis of immunotactoid GN

Same microtubular crystal-like organization in leukemic lymphocytes and in the capillary wall suggests abnormal properties of the monoclonal IgG (4/5 patients with CLL)



Kidney





Bridoux et al, Kidney Int, 2002 62:1764

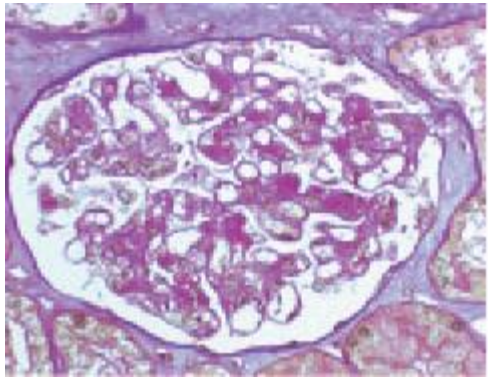
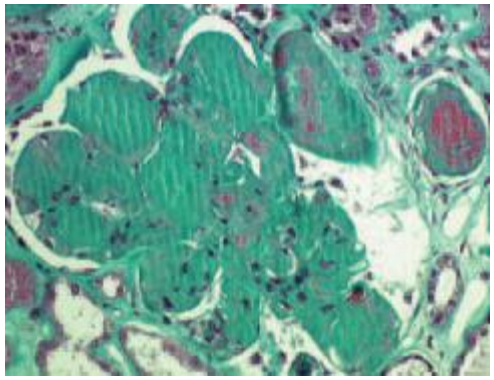
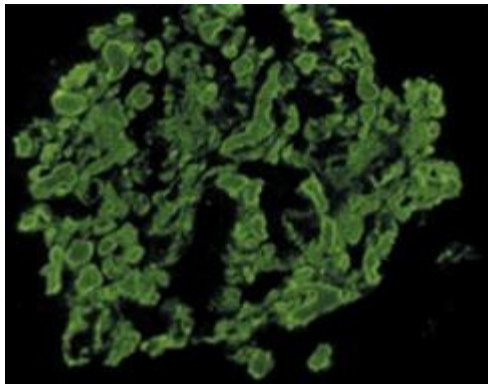
Pathogenesis of immunotactoid GN

- **Aggregation or crystallization of monoclonal Ig may be due to:**
  - **autoreactivity**
  - **reactivity with an as yet unknown antigen**
  - **structural abnormalities**

- **No sequence abnormalities in two patients (*Bridoux et al, Kidney International 2002*)**

- **Animal model : CD2AP haploinsufficiency induces immuno tactoid deposits, but only in the mesangium (*Kin et al, Science 2003, 300:1298*)**

IgM-secreting monoclonal proliferations (including Waldenström macroglobulinemia)

First described by Morel-Maroger as « Waldenström macroglobulinemic glomerulonephritis » (decreased incidence)

Histologic lesions are diverse and may occur in benign IgM

Intracapillary deposits of IgM with or without cryoglobulinemia
AL-amyloidosis
Immunotactoid glomerulopathy
Nonamyloid fibrillary glomerulopathy
Cryoglobulinemia-related glomerulonephritis
MPGN without cryoglobulinemia
Crescentic glomerulonephritis
LCDD

Higgins et al, CJASN 2018,13:1037 (Mayo Clinic)

Investigating glomerular involvement in a patient with CLL, related B-cell lymphoma and WM

- **Kidney biopsy :**
  - **establish monoclonality of deposited Ig with anti-LC, anti-HC and anti-IgG subclass antibody (blood M-component often undetectable)**
  - **determine ultrastructure (organization) of the deposits**

- **Serum :**
  - **cryoglobulinic activity**
  - **M-component (IF, FLC assay)**

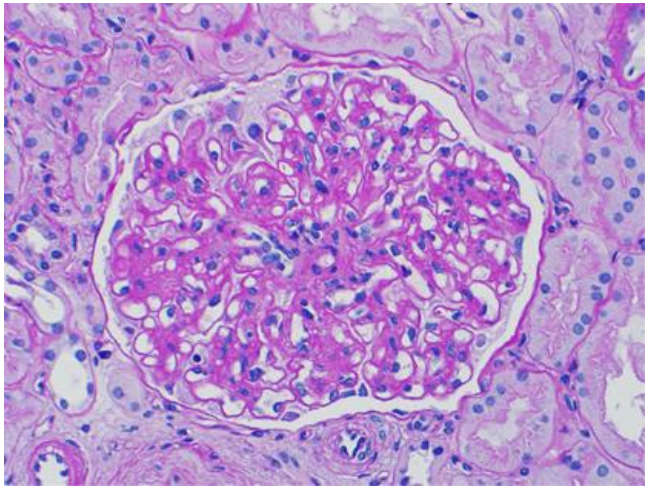
- **Bone marrow and blood lymphocytes :**
  - **clonality**
  - **inclusions**

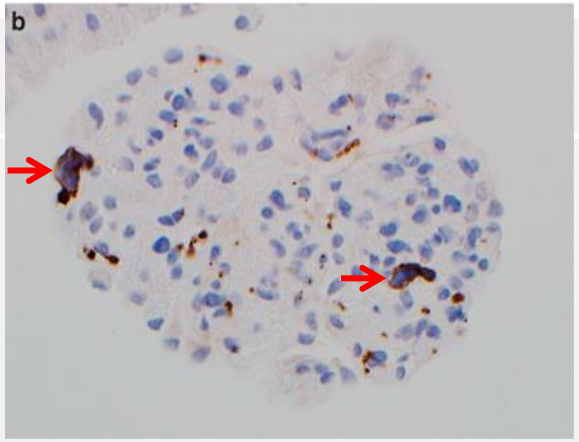
Myeloproliferative neoplasm-associated glomerulopathies

- **Clonal hematopoietic stem cell disorders characterized by expansion of myeloid lineages**
- **11 patients reported by Said et al (D'Agati's group)**
- **Mean time from diagnosis of the neoplasms to biopsy : 7.2 years**
- **Mesangial sclerosis and hypercellularity (n=11), segmental sclerosis (n=8), features of TMA (n=9), intracapillary hematopoietic cells (n=4)**
- **Follow-up : 7 pts with persistent renal dysfunction, 4 pts progressing to ESRD**

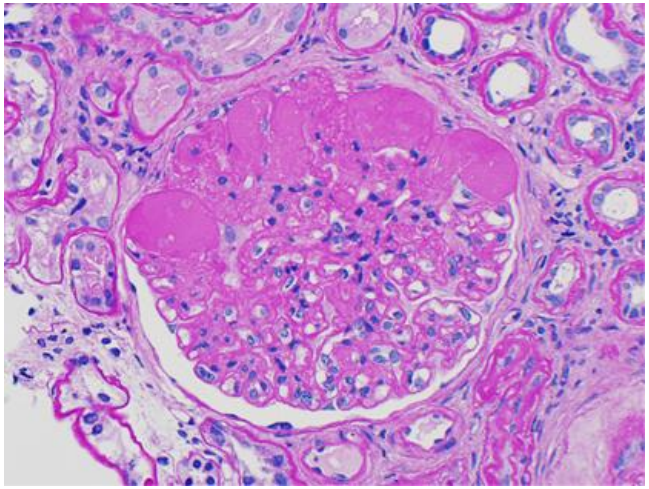
Said et al, KI 2011, 80 : 753

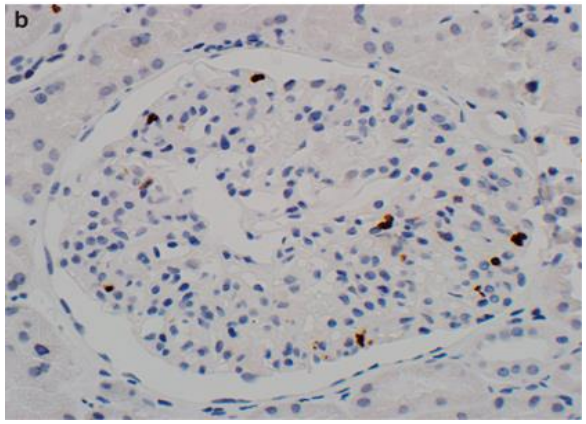
Glomerular lesions associated with myeloproliferative neoplasms





Intracapillary megakaryocytes/platelets

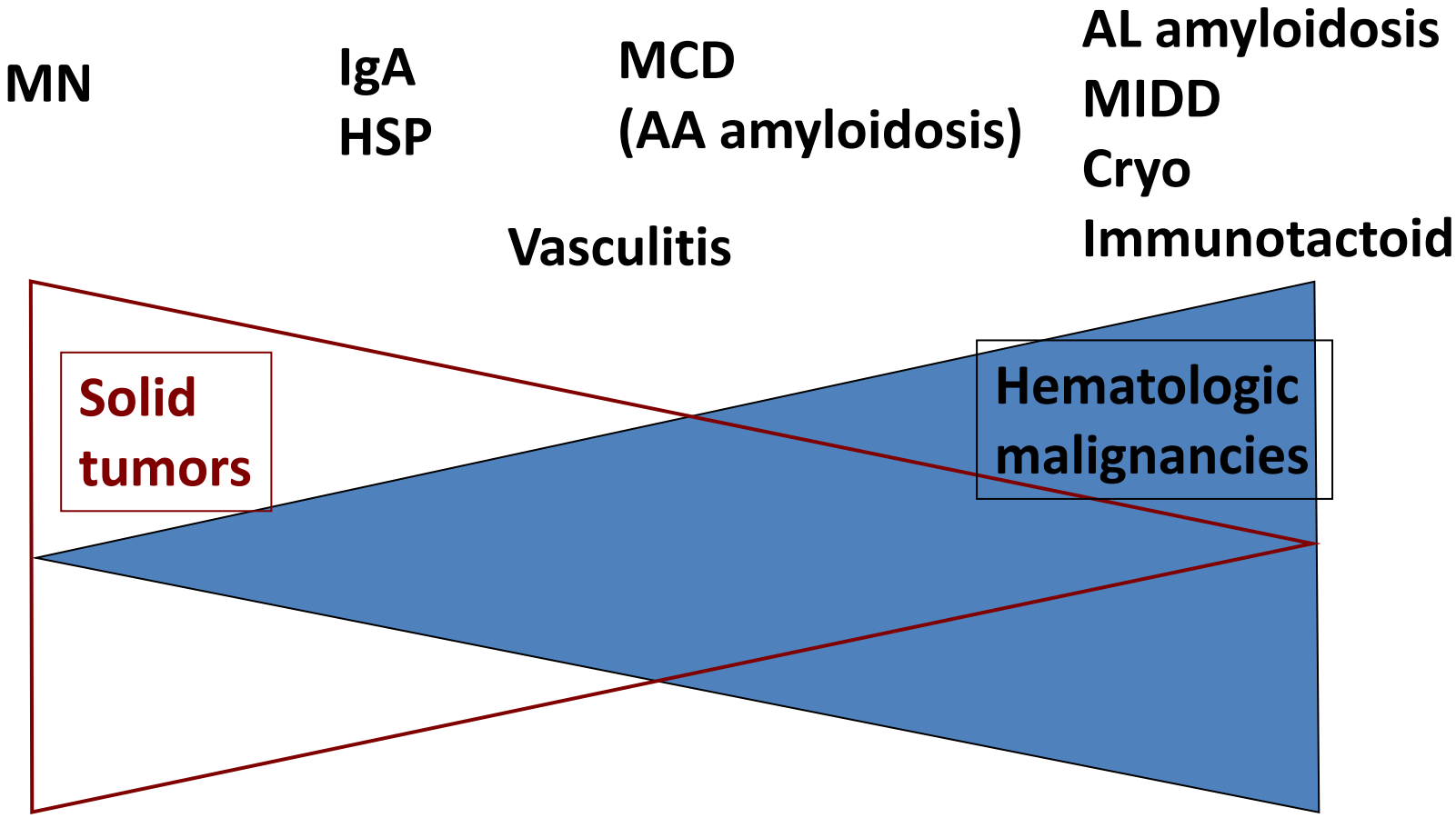




Intracapillary immature granulocytes

Said et al, KI 2011, 80 : 753

The spectrum of cancer-related glomerulopathies



Glomerular lesions associated with chemotherapy

Endothelial damage (TMA)

Mitomycin C, gemcitabine, anti-VEGF agents, TKI, mTOR inhibitors, calcineurin inhibitors

Epithelial (podocyte) damage

Collapsing FSGS: pamidronate, mTOR inhibitors, calcineurin inhibitors, interferons α, β, and γ, adriamycin

FSGS NOS: interferons α, β, and γ, calcineurin inhibitors, mTOR inhibitors, daunorubicin

Minimal change disease: pamidronate, interferons α, β, and γ, daunorubicin

MPGN: anti-VEGF agents

Crescentic GN: GM-CSF

Lupus-like nephritis: ipilimumab

Jhaveri et al, KI 2013, 84 : 34

HSCT-related glomerular diseases

- **Glomerular diseases and chronic GVHD**
  - **Membranous nephropathy (MN)**
  - **Minimal change disease (MCD)**
  - **Focal segmental glomerulosclerosis (FSGS)**

- **Thrombotic microangiopathy following HSCT**
  - **CNIs**
  - **Allogeneic transplantation**
  - **Total body irradiation**
  - **High-dose chemotherapy**

Conclusions

- **Clear links between cancer and associated glomerulopathies although the nature of the link remains obscure in solid tumors**

- **Diagnosis of cancer-associated glomerulopathy is of crucial importance because :**
  - **the glomerulopathy may reveal the cancer (hematologic malignancy)**
  - **the glomerular disease usually regress with the complete remission of the malignancy**

- **These rare tumour complications may help to unravel the pathophysiology of more common diseases**

- **Chemotherapy and HSCT-related glomerulopathies should also be considered**

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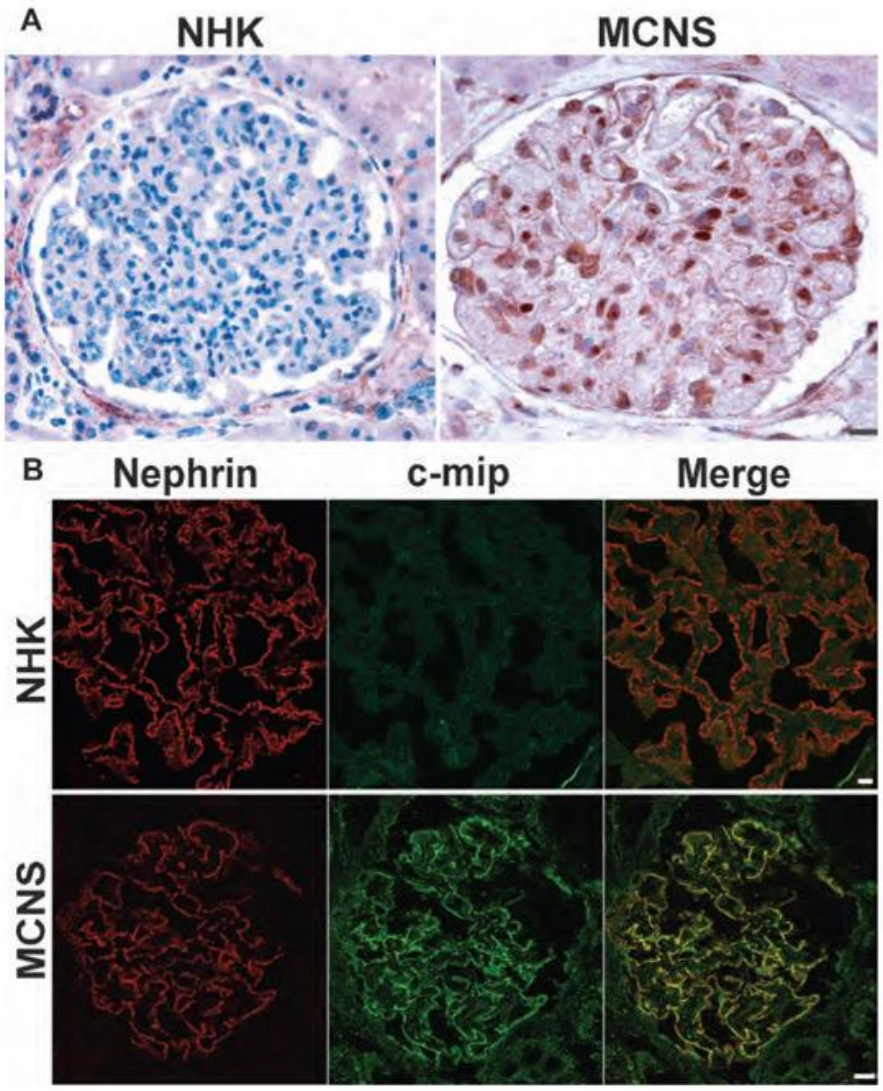
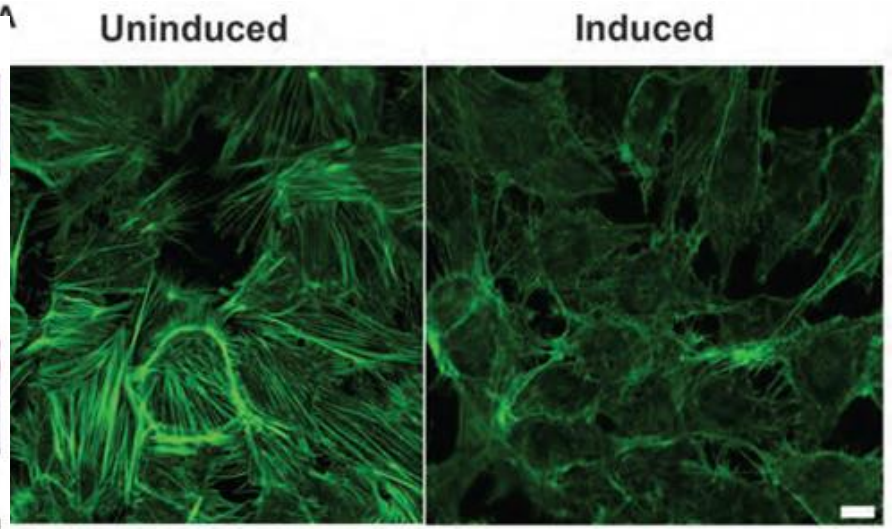
Pathophysiology of MCD in Hodgkin lymphoma

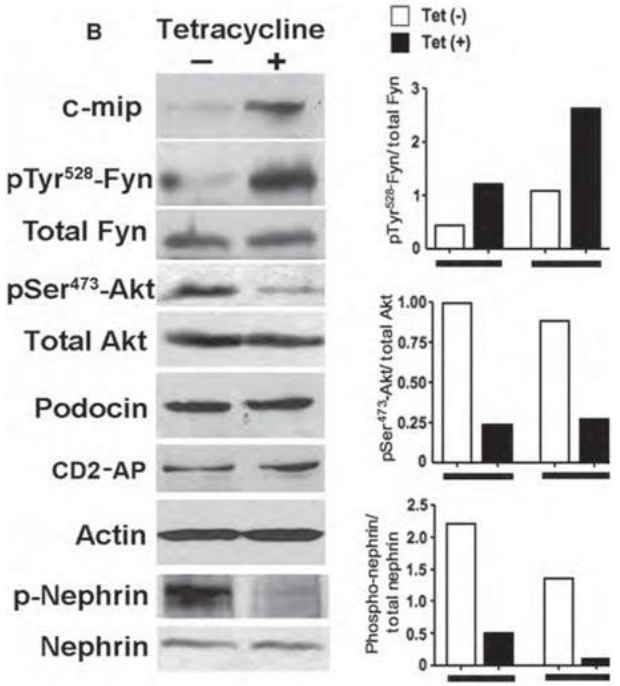
- Putative circulating factor secreted by T Lymphocytes

- Role of c-maf-inducing protein (*c-mip*)

Pathophysiology of MCD in Hodgkin lymphoma

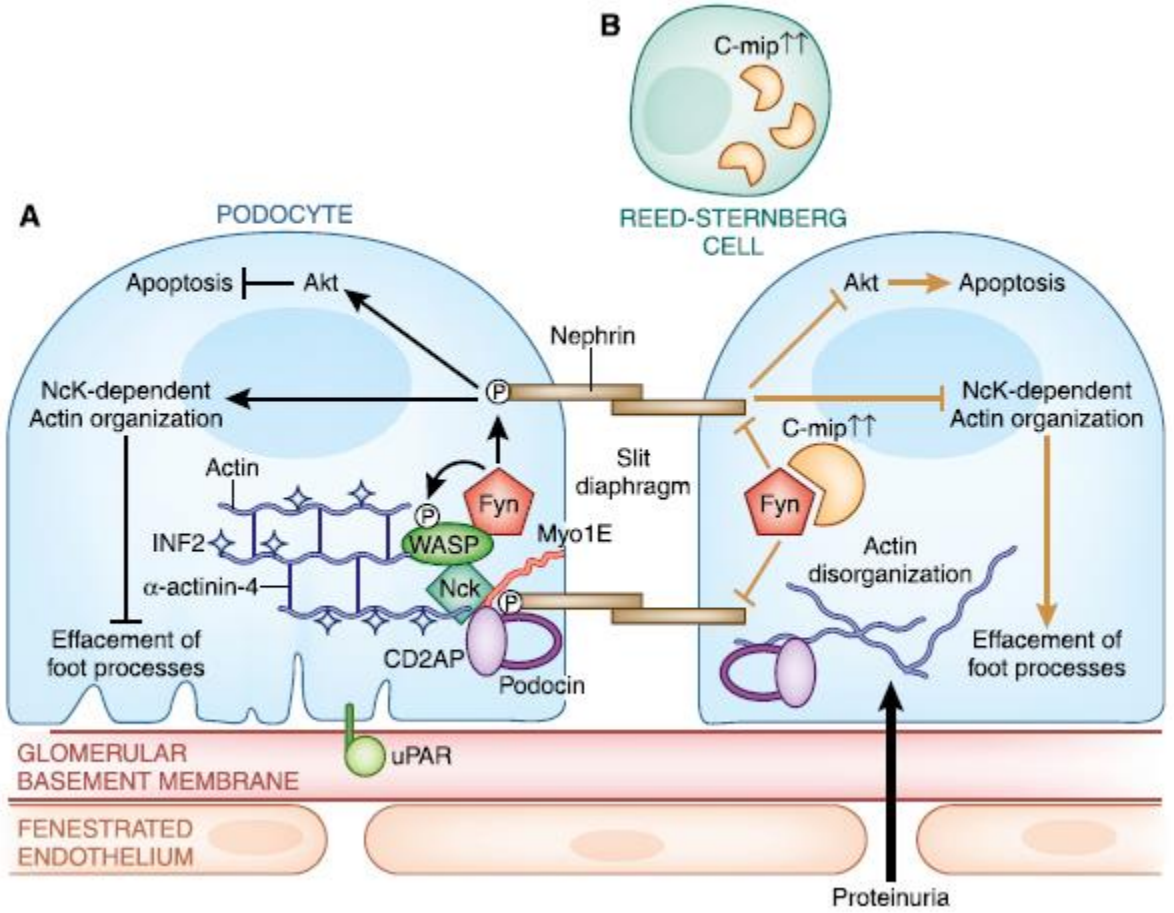






Zhang SY, Sci Signal, 2010, 3:ra39

An hypothetical mechanism of nephrotic syndrome (MCD) in Hodgkin lymphoma



Cambier et al, Clin JASN, 2012 7:1701