Secondary GN's

Salwa Bakkali , DO , PGYIII

Jeff Kaufhold MD FACP Oct 2021

Case of TM

- 48 y o F with poorly controlled DM of 13 years and HTN that presents with rapidly progressive renal failure , non- nephrotic range proteinuria and hematuria.

- PMH : CABG X 5, bilateral lower ext arterial stenosis repair, CCK, CVA, ovarian cancer 2006
- PSH : TAH BSO 2006
- PFH : ovarian cancer.
- SH : =35 P/Y, Occ ETOH and no drug use , factory worker

Case of TM

Labs :

Cr 1.4 mg% (1/2013)

Cr 2.4 mg% (5/2013)

Cr 4.2 mg% (3/2014)

Renal US normal

CT abdomen/pelvis : stable pulmonary nodules and new mass in the pelvis

- Micro exam: dysmorphic RBCs

Path report

- Moderate interstitial fibrosis and tubular atrophy involving approximately 30% of the renal cortex. A patchy mild mixed interstitial inflammatory infiltrate is seen
- **Fibrillary glomerulopathy.**
- Congo red negative

Questions

- Regarding diabetic nephropathy which is FALSE ?
  - A. 20 % of pts develop ESRD after 20 years of initial diagnoses with DM
  - B. Diabetic nephropathy precedes retinopathy usually
  - C. The predominant structural changes include mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis.

- Diabetic nephropathy :
  - Mesangial expansion, GBM thickening, and glomerular sclerosis.
  - Degree of albuminuria
- ESRD 4 to 17 % at 20 years
  - 16 % at 30 years
- Pt with Nephropathy -> diabetic microvascular disease
- The retinopathy typically precedes the onset of overt nephropathy in these patient

Why not diabetes ?

Fibrillary GN

- Rare disease (0.5 to 1 % of native renal biopsies)
- Glomerular accumulation of nonbranching, randomly arranged fibrils that are ultra structurally indistinguishable from amyloid fibrils
- Congo red-negative
- Difference from amyloid
- Nephrotic range proteinuria +RPRF

Clinicopathologic features that distinguish fibrillary glomerulonephritis from morphologically similar immunopathologic features of fibrillary/microtubular glomerulopathies

Characteristic	Amyloid	Fibrillary Glomerulonephritis	Immunotactoid Glomerulopathy
Appearance	Fibrils	Fibrils, rarely microtubular	Microtubules
Fibril/microtubule size (nm)	8 to 15 (most often 8 to 12)	12 to 24 (most often 18 to 20)	>30 (most often 34 to 49)
Fibril arrangement in tissues	Random	Random	Often organized in parallel arrays
Reactions with histochemical dyes Congo Red and Thioflavin T	Yes	No	No
Ig deposition	Monoclonal light chains in AL type amyloid only	Usually polyclonal, occasionally oligoclonal or monoclonal IgG	Monoclonal or oligoclonal IgG common
Association with lymphoplasmacytic disorders	Yes, if AL type	Uncommon	Common

Disease progression

- 40 to 50 % of pts with FGN or immunotactoid glomerulopathy develop ESRD within short time period.

- 7 months with diffuse sclerosing glomerulonephritis
- 20 m with diffuse proliferative glomerulonephritis
- 44 m with membranoproliferative glomerulonephritis
- 80 m with mesangioproliferative/sclerosing disease
- 87 m with membranous glomerulonephritis

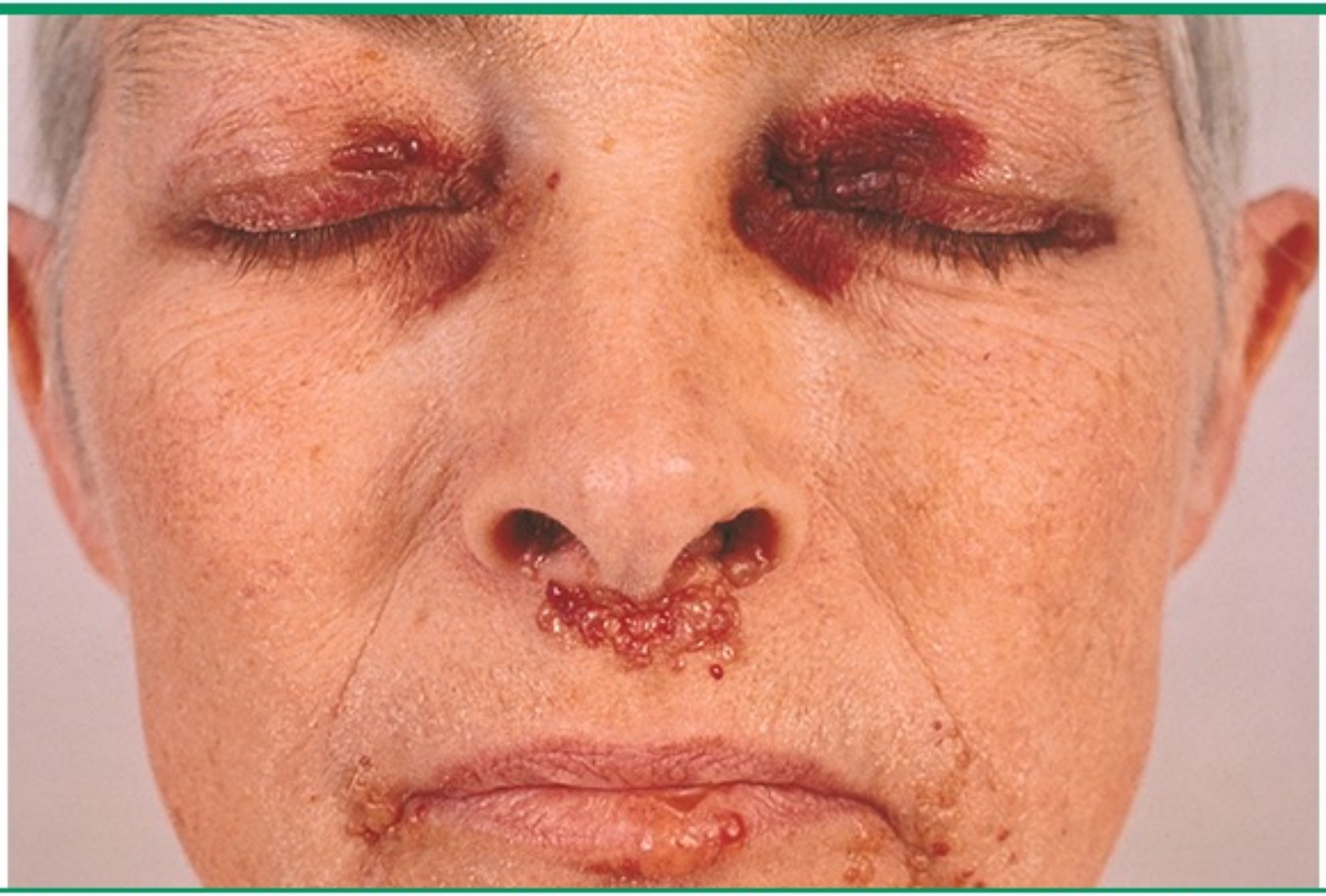
Disease Progression

Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features. Rosenstock JL, et al . Kidney Int. 2003;63(4):1450

- Purpura, characteristically elicited in a periorbital distribution (raccoon eyes) by a Valsalva maneuver or minor trauma is highly characteristic of what disease process ?

Question ?

Primary amyloid affecting facial skin and eyelids



In this patient with primary amyloidosis, amyloid deposits are seen below the nose, around the lips, and on the eyelids. These lesions are waxy and raised, and they show characteristic hemorrhage. This patient also had severe amyloid arthritis and eventually developed a malignant plasma cell dyscrasia.

Amyloid GN

- Primary amyloidosis usually associated with a monoclonal gammopathy.
- Pts usually > 40 .
- Primary amyloidosis accounted for 10% of cases of nephrotic syndrome in patients >44 compared with only 1% in younger patients.

- What sites can be biopsied to confirm amyloid diagnoses?
  - A. fat pad
  - B. rectal mucosa
  - C. tongue
  - D. kidney
  - E . All of the above.

AMYLOID

AMYLOID

- Aspiration biopsy of subcutaneous fat with Congo red staining and examination using polarizing microscopy has a sensitivity of 57 to 85 percent and a specificity of 92 to 100 percent for primary (AL) or secondary (AA) amyloidosis

AMYLOID

- AL or primary amyloid : a light chain dyscrasia in which fragments of monoclonal light chains form the amyloid fibrils;
- AA or secondary amyloidosis: the acute phase reactant serum amyloid A forms the amyloid fibrils.
- AA amyloid is associated with a chronic inflammatory disease

What are the main distinguishing features of amyloid versus fibrillary GN ?

- 70 % hematuria
- 100 % proteinuria with nephrotic syndrome
- 70 to 75 % proteinuria
- Renal insufficiency (serum creatinine ≥1.5 mg/d) in 50 to 55 %
- Hypertension in 65 to 70 %
- Mean age 50 years

Fibrillary GN symptoms

Associated conditions

- 30 % of pts autoimmune disease :
- Hashimoto thyroiditis
- RA
- Ankylosing spondylitis
- Urticarial vasculitis

MALIGNANCIES.

Table 1. Clinical Characteristics at the Time of First Kidney Biopsy

Case No.	Sex	Age (y)	High BP	Proteinuria (g/d)	NS	Microscopic Hematuria	eGFR (mL/min/1.73 m^2)	Associated Medical Condition
1	M	62	+	11.4	+	+	24	COPD
2	F	68	+[a]	4.5	+	NA	34	—
3	M	25	−	1.8	−	+	87	Down syndrome
4	M	71	+	5.2	+	+	33	T2DM
5	M	45	−	2.5	−	+	97	—
6	F	58	+	6.5	−	−	61	T2DM
7	M	61	+	1.7	−	+	55	COPD
8	M	56	+	1.7	−	+	42	T2DM/MGUS
9	M	82	+	6.0	+	+	24	Colon carcinoma
10	M	41	−	17.0	+	−	39	T2DM/COPD
11	M	73	+	0.5	−	+	35	T2DM/AIHA
12	F	59	+	1.0	−	+	64	—
13	M	61	+	0.7	−	+	86	—
14	M	61	−	2.6	−	+	115	Hepatitis C
15	F	67	+	6.0	+	+	20	—
16	F	68	+	3.2	—	—	47	—
17	M	52	—	8.0	+	+	49	COPD
18	F	54	+	3.5	+	—	22	—
19	M	72	—	2.0	—	—	66	Type II Cryo/COPD
20	M	30	+	7.6	—	+	39	Psoriasis
21	M	67	+	0.8	—	+	96	Rheumatoid arthritis
22	F	33	—	4.2	+	—	57	Hashimoto thyroiditis
23	M	53	—	1.6	—	+	35	Hepatitis C/T2DM
24	F	46	+	2.5	—	+	67	Ankylosing spondylitis
25	F	46	+	0.5	−	−	77	HUVS
26	F	63	+	3.8	+	+	30	Hashimoto thyroiditis
27	F	56	+	4.5	+	+	87	Graves disease
Median [range]		59 [25-82]		3.2 [0.5-17]			49 [20-115]	

Note: Cases 1-7, 16, and 18 have been published elsewhere.[4]

Abbreviations: AIHA, autoimmune hemolytic anemia; COPD, chronic obstructive pulmonary disease; Cryo, cryoglobulinemia; eGFR, estimated glomerular filtration rate; BP, blood pressure; HUVS, hypocomplementemic urticarial vasculitis syndrome; MGUS, monoclonal gammopathy of undetermined significance; NA, not available; NS, nephrotic syndrome; T2DM, type 2 diabetes mellitus.

[a]Malignant hypertension with diastolic blood pressure >130 mm Hg and papillary edema.

Associated conditions

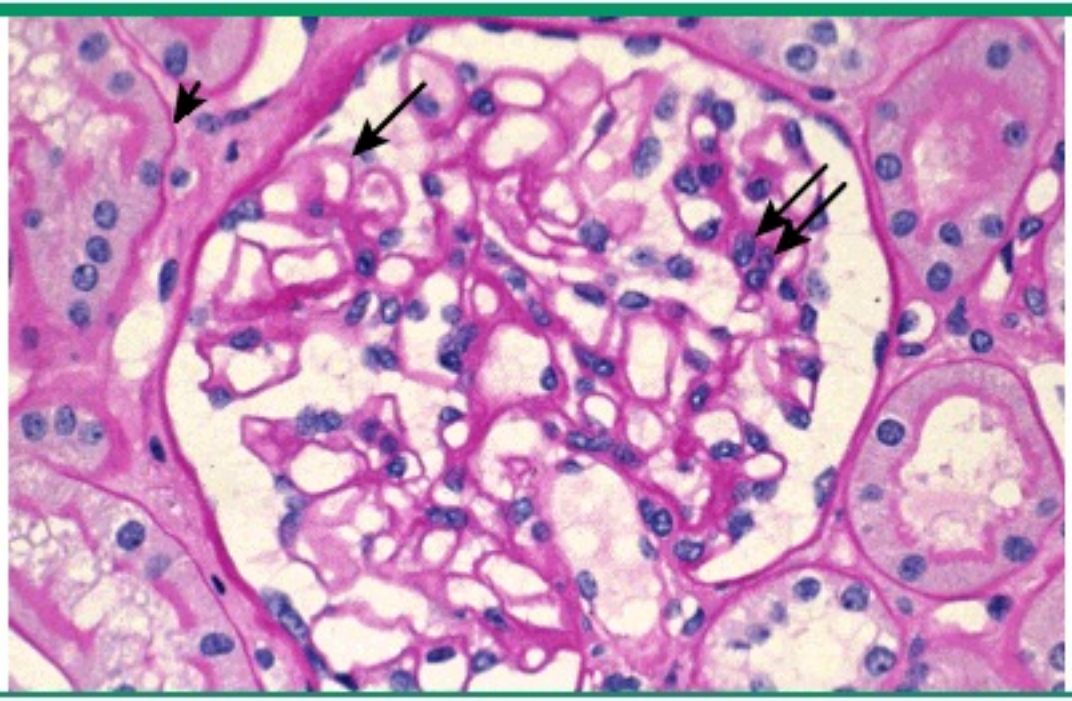
- 15 pts (23 %) had an associated malignancy, which was diagnosed 15 Y before to 10 Y after the onset of renal disease .
- 17 of the 25 malignancies were due to MM or leukemia.
- 11 pts (17 %) had a monoclonal gammopathy
- 10 pts (15 %) had autoimmune disorders

Fibrillary glomerulonephritis: a report of 66 cases from a single institution.. Mayo clinic

Diagnosis of FGN

- Congo red negative
- Mesangial immnuglobulin IgG deposits into randomly arranged fibrils of 10-30 mm .
- Immunofluoresence : deposits are composed of mainly polyclonal IgG4
  - Light microscopy: not specific , predominant pattern of membranoprolifeative GN or membranous GN.

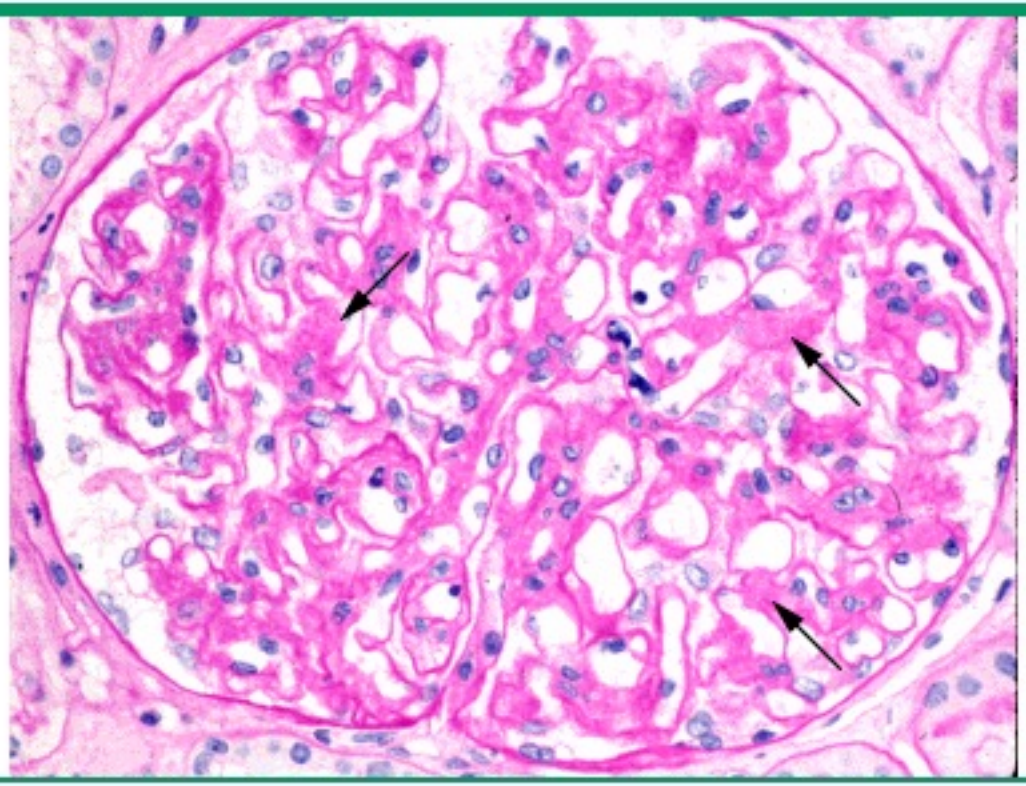
Normal glomerulus



Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

Courtesy of Helmut G Rennke, MD.

Fibrillary glomerulonephritis



Light micrograph in fibrillary glomerulonephritis shows diffuse expansion of the mesangium by amorphous, acellular material (arrows). Electron microscopy and Congo red staining are necessary to distinguish this light microscopic appearance from amyloidosis or light chain deposition disease.

Courtesy of Helmut Rennke, MD.

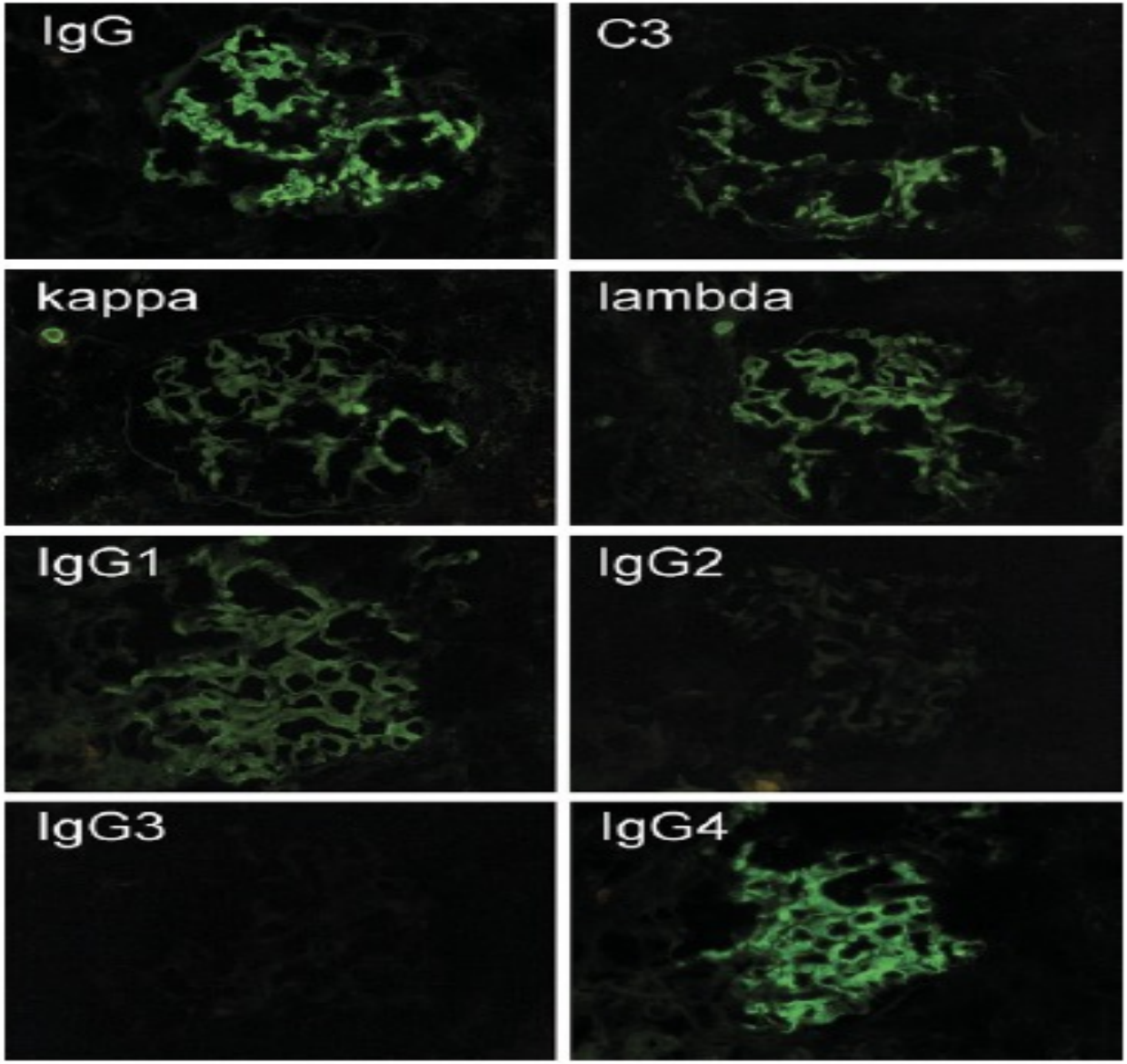
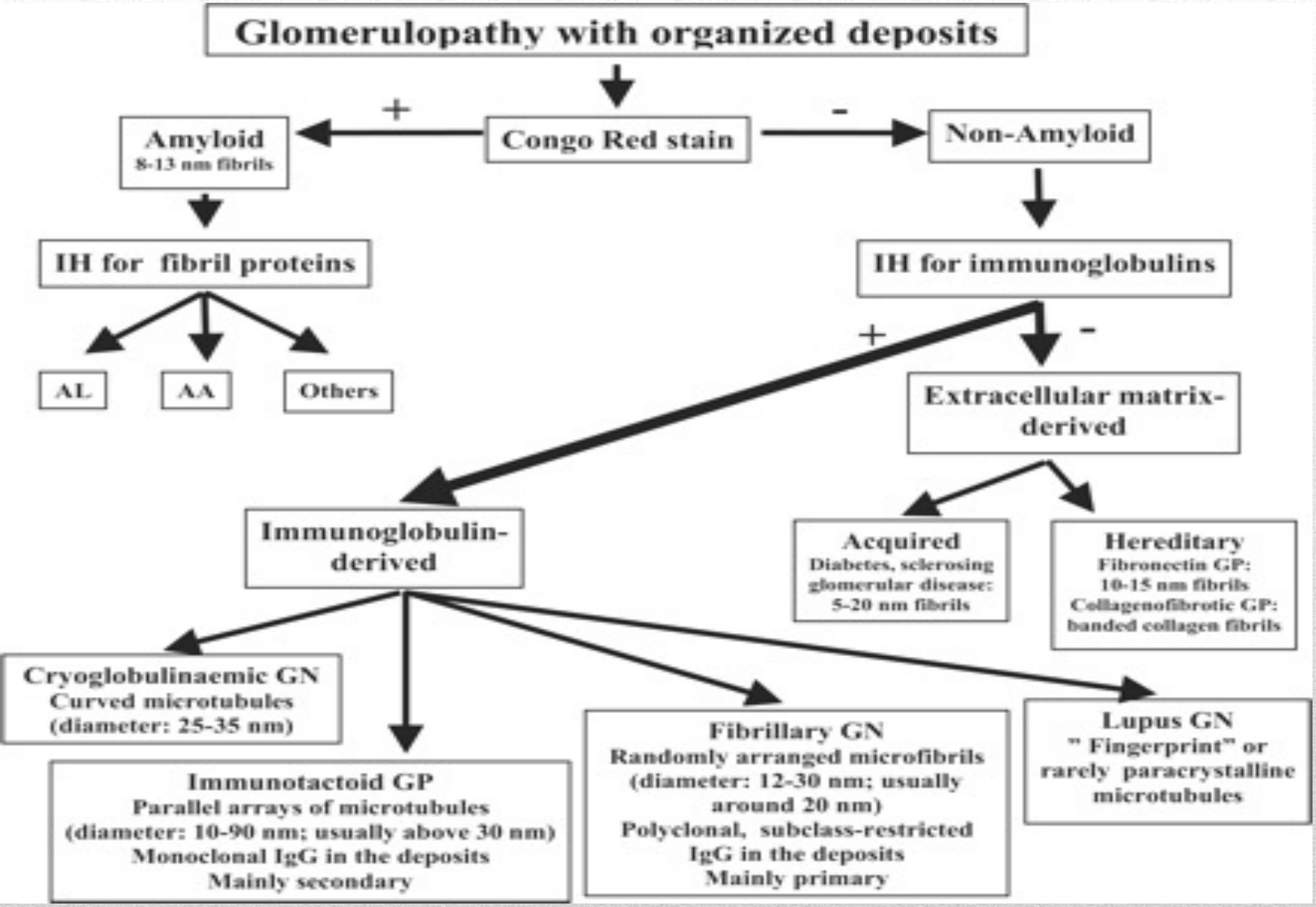


Figure 2. Immunofluorescence microscopy. Kidney biopsy, immunofluorescence staining for total immunoglobulin G (IgG), C3, κ and λ light chain, IgG1, IgG2, IgG3, and IgG4 (patient 14). Diffuse staining of the mesangium and glomerular capillary walls with conjugates specific for IgG, C3, and κ and λ light chain.


Glomerulopathy with organized deposits
+
-
Amyloid
8-13 nm fibrils
Congo Red stain
Non-Amyloid
IH for fibril proteins
IH for immunoglobulins
AL
AA
Others
+
-
Extracellular matrix-derived
Immunoglobulin-derived
Acquired
Diabetes, sclerosing glomerular disease:
5-20 nm fibrils
Hereditary
Fibronectin GP:
10-15 nm fibrils
Collagenofibrotic GP:
banded collagen fibrils
Cryoglobulinaemic GN
Curved microtubules
(diameter: 25-35 nm)
Immunotactoid GP
Parallel arrays of microtubules
(diameter: 10-90 nm; usually above 30 nm)
Monoclonal IgG in the deposits
Mainly secondary
Fibrillary GN
Randomly arranged microfibrils
(diameter: 12-30 nm; usually around 20 nm)
Polyclonal, subclass-restricted IgG in the deposits
Mainly primary
Lupus GN
" Fingerprint" or rarely paracrystalline microtubules

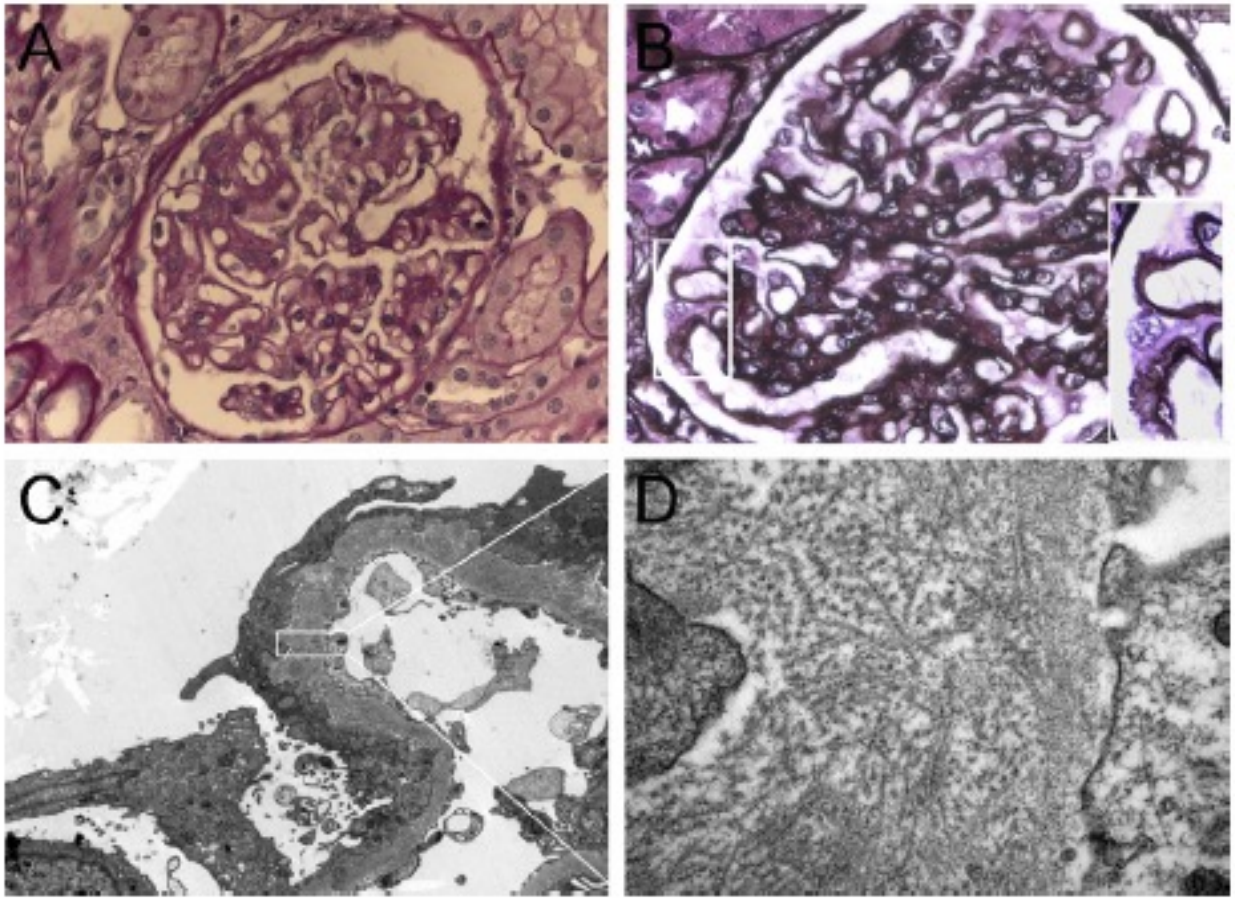
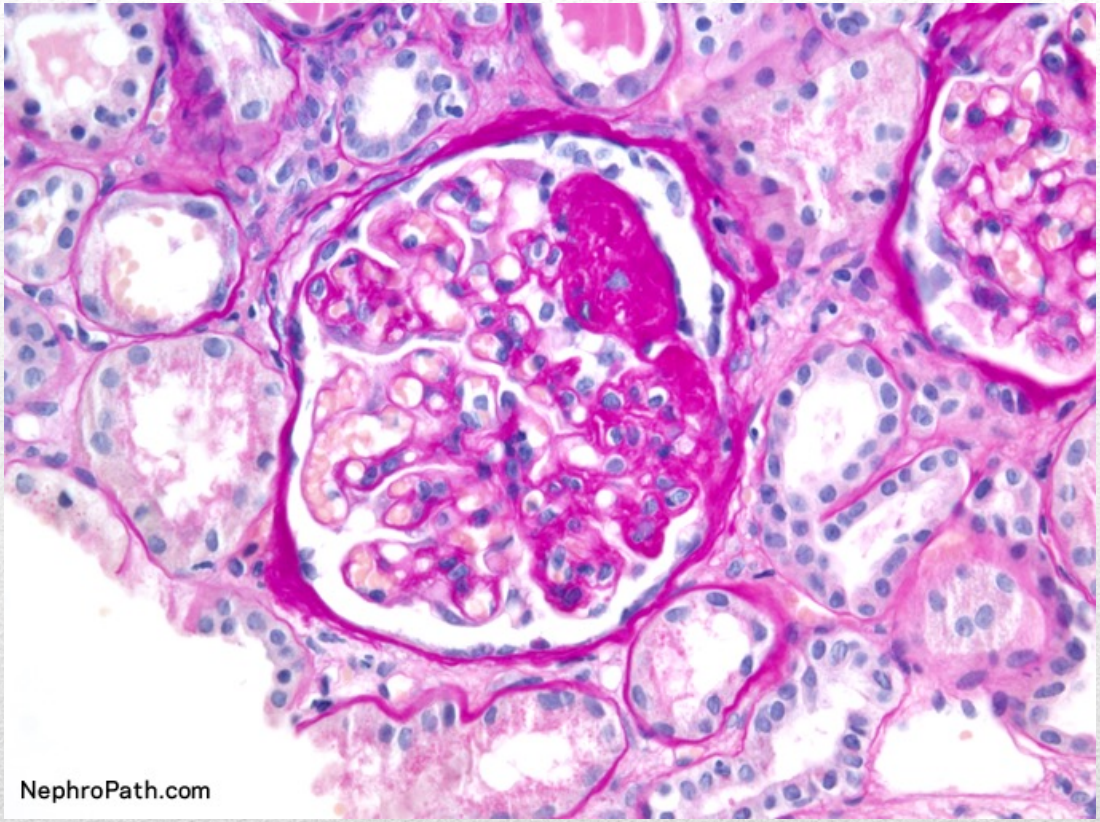


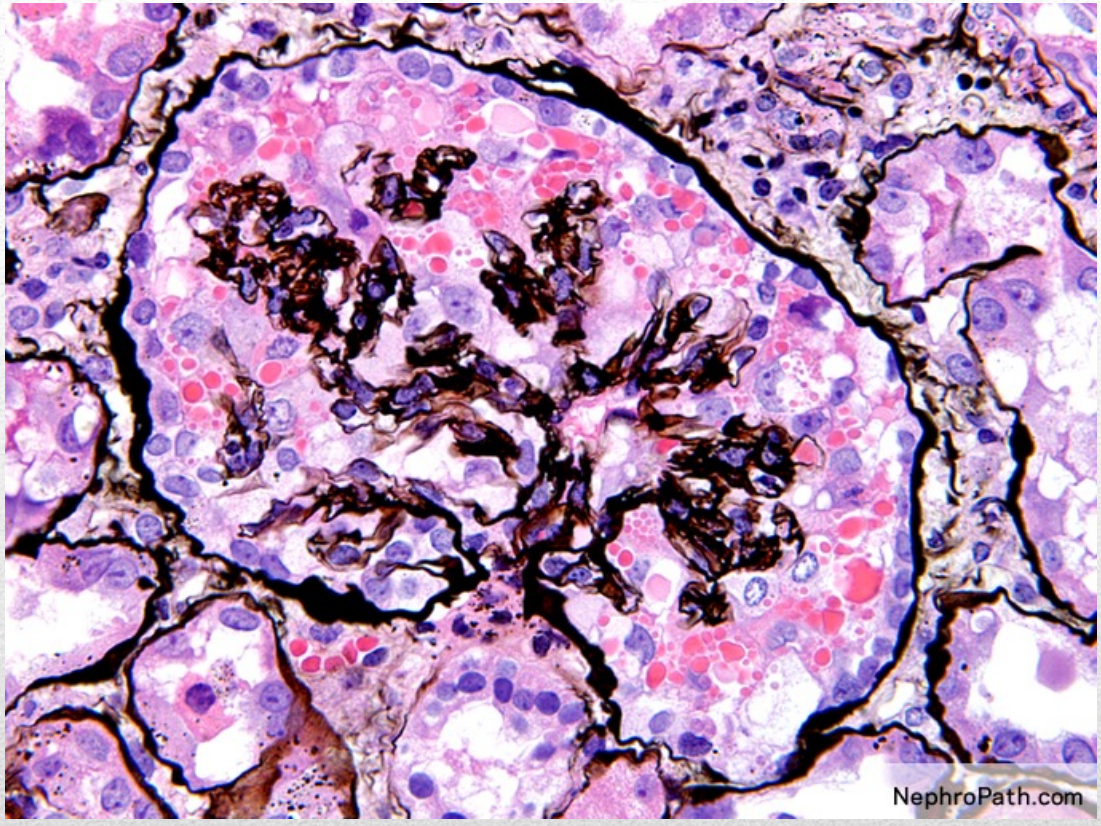
Figure 1. Mesangial glomerulonephritis. (A, B) Kidney biopsy, light microscopy. (A) Glomerulus shows mesangial expansion by periodic acid–Schiff (PAS)-positive material and segmental thickening of glomerular capillary walls, without increased glomerular cellularity (patient 14; PAS staining; original magnification, ×200). (B) Focal and segmental glomerular capillary wall thickening with "spikes." Mesangial deposits were not stained with silver impregnation (patient 17; Marinozzi silver staining; original magnification, ×400). Inset: high-power oil-immersion view of the markedly thickened capillary wall shows spikes (Marinozzi silver staining; original magnification, ×1,000). (C, D) Kidney biopsy, electron microscopy (patient 13). (C) Intra- and epimembranous fibrillary deposits with thickening of the glomerular capillary wall (original magnification, ×10,000). (D) Deposits were composed of randomly oriented fibrils of 16.1 ± 0.6 nm in external diameter, without distinct hollow core (original magnification, ×100,000).

Other kidney diseases with Fibrils

- Not to be confused with:
  - HIV nephropathy
  - Fabry's Disease
  - Myeloma



Secondary FSGS



HIV Nephropathy. Collapsing FSGS

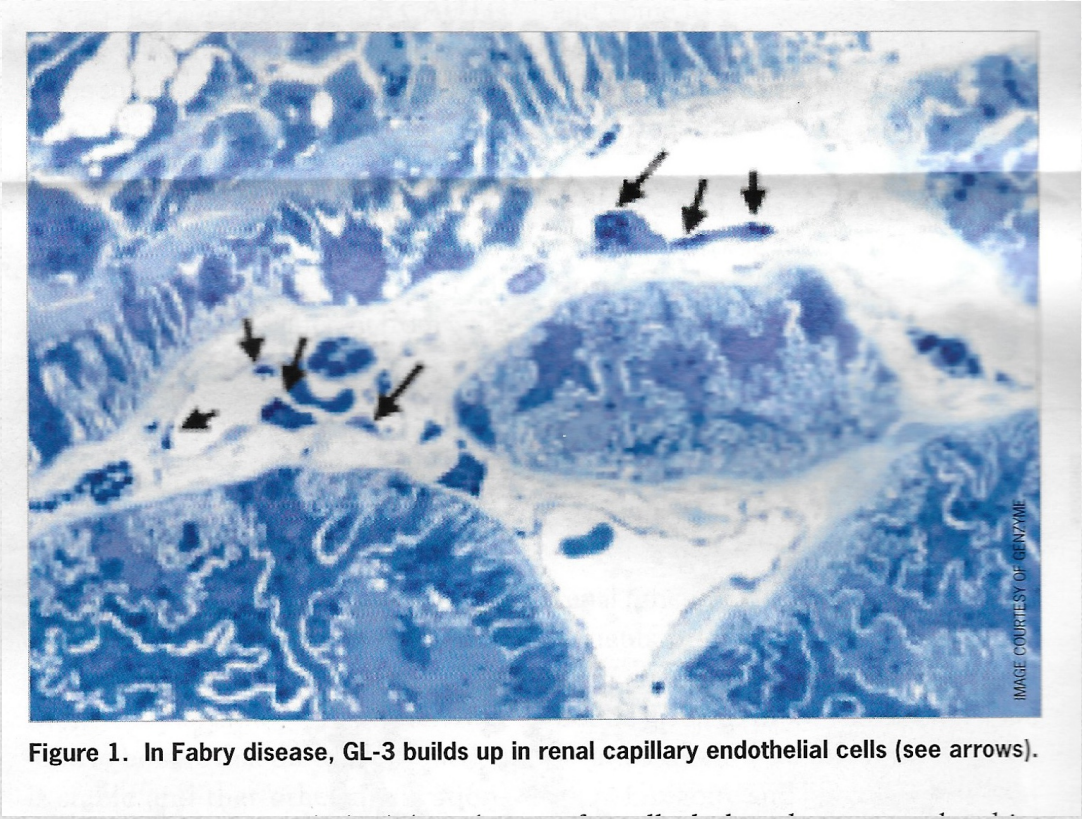
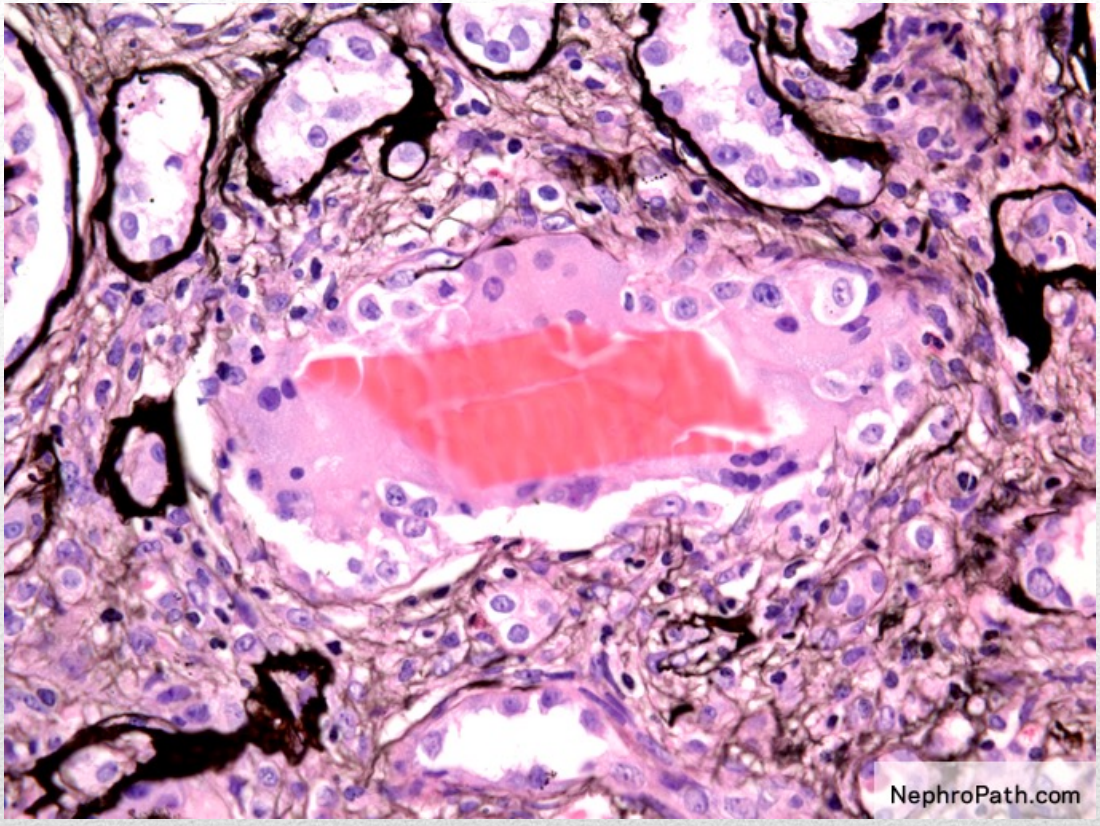


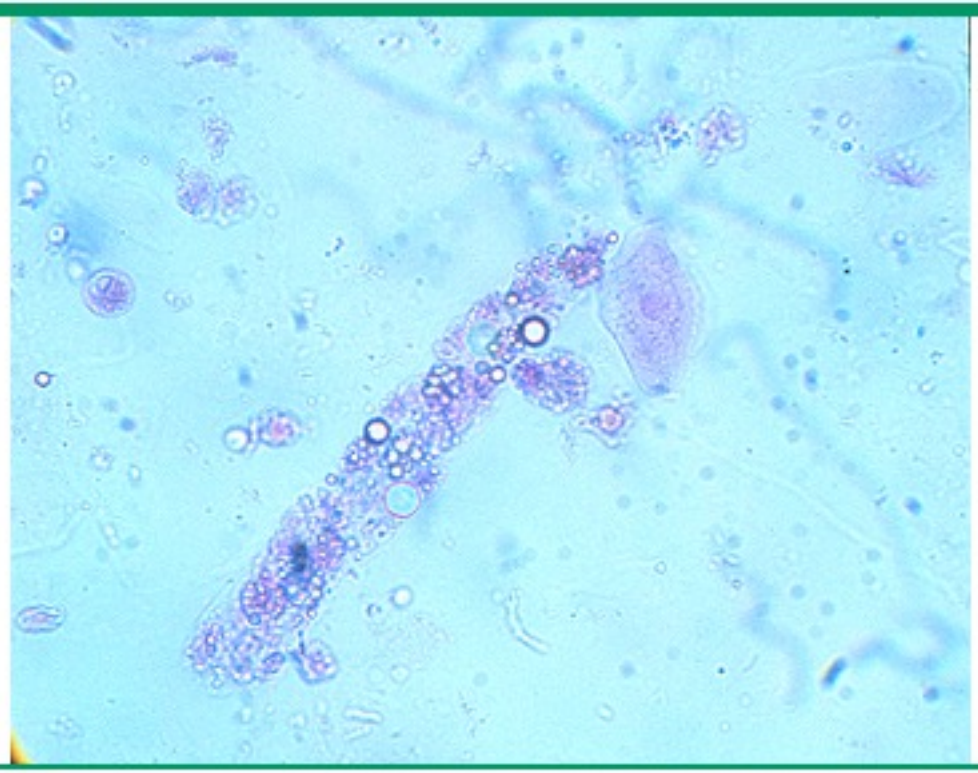
Figure 1. In Fabry disease, GL-3 builds up in renal capillary endothelial cells (see arrows).

Fabry's



Light chain cast in Myeloma

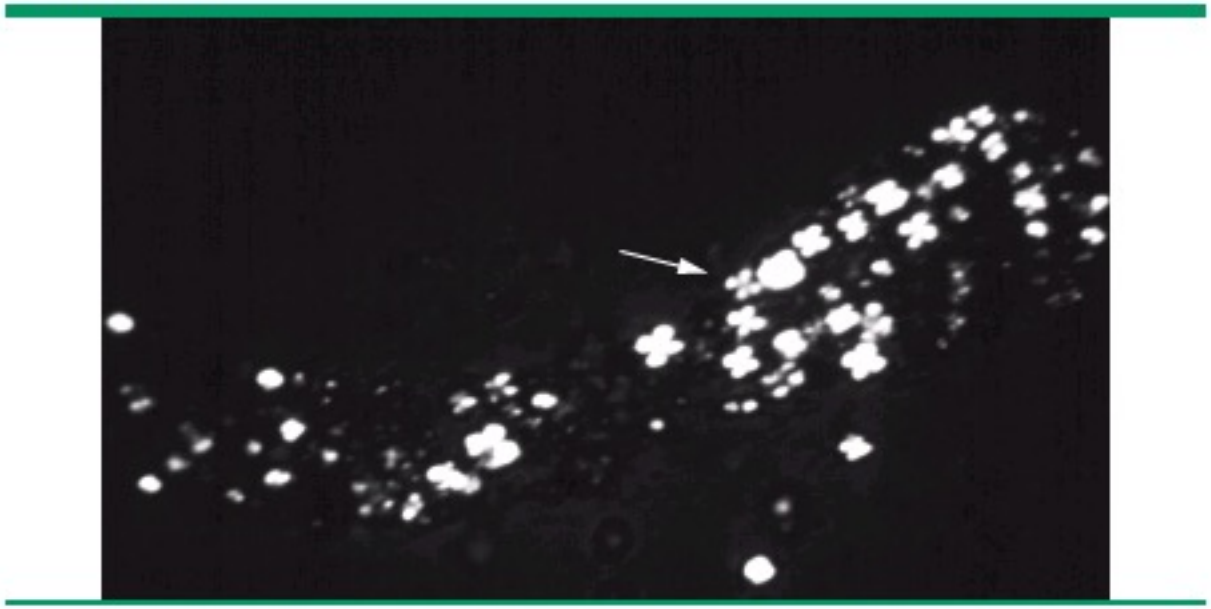
Fatty cast



Urine sediment showing a fatty cast. The fat droplets (or globules) can be distinguished from red cells (which also have a round appearance) by their variable size (from much smaller to much larger than a red cell), dark outline, and "Maltese cross" appearance under polzarized light.

Courtesy of Frances Andrus, BA, Victoria Hospital, London, Ontario.

Fatty cast



Urine sediment showing fatty cast under polarized light. The fat droplets have a characteristic "Maltese cross" appearance (arrow).

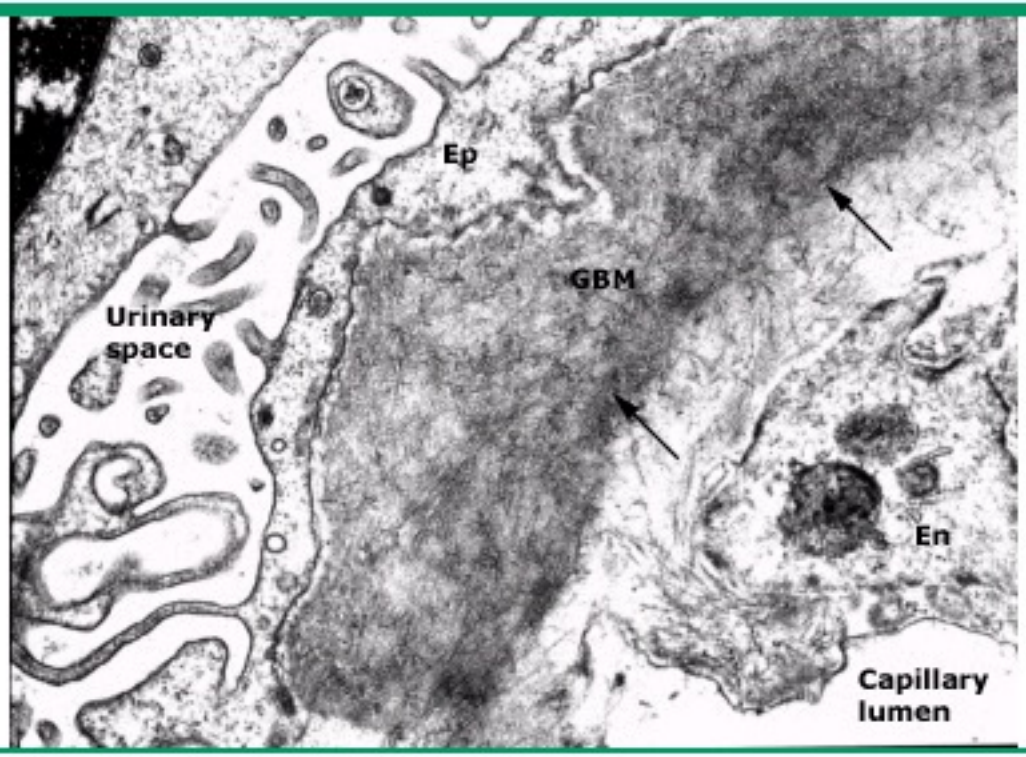
Courtesy of Harvard Medical School.

UpToDate®

Complications of Fibrillary GN

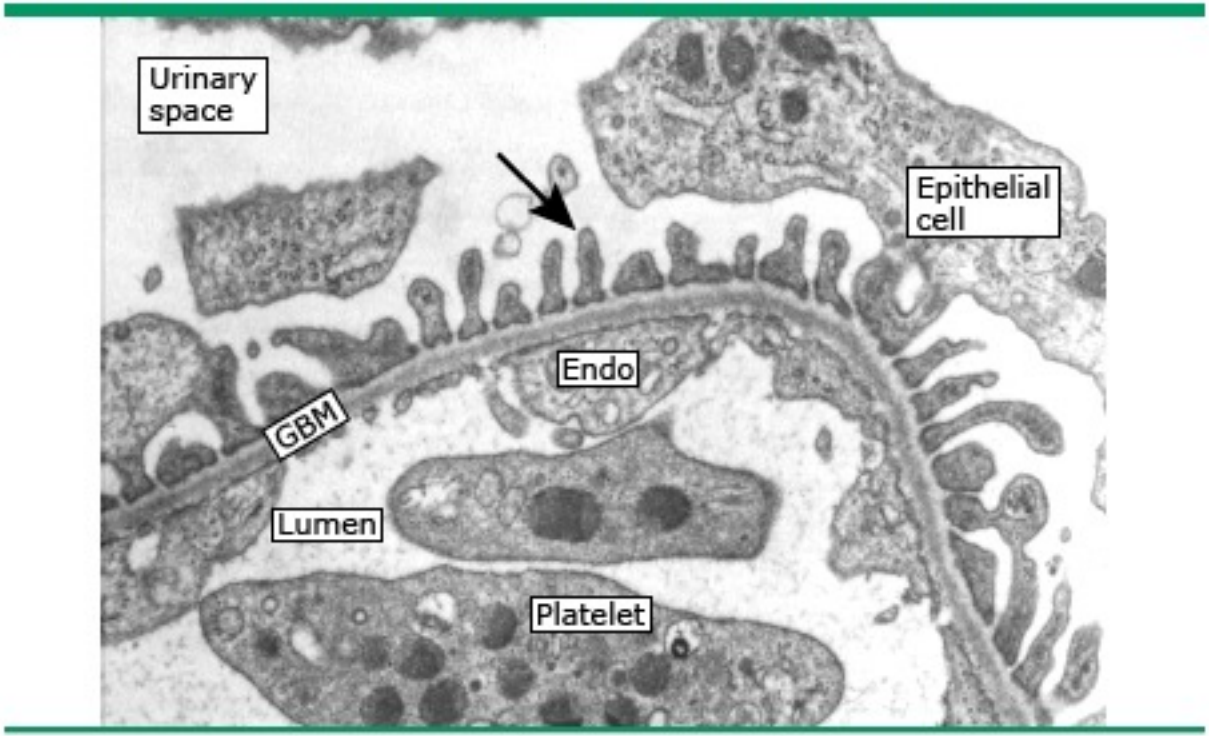
- Protein malnutrition
- Hypovolemia
- Thromboembolism (10-40 % increased incidence of arterial and venous thrombosis)

Fibrillary glomerulonephritis EM



Electron micrograph in fibrillary glomerulonephritis showing intramembranous and subendothelial fibrillary deposits (arrows). The glomerular basement membrane (GBM) is markedly disrupted by the infiltrating fibrils and a distinct lamina densa cannot be seen.
En: endothelial cell; Ep: epithelial cell.
Courtesy of Helmut Rennke, MD.

Electron micrograph of a normal glomerulus



Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin, and no electron-dense deposits are present. Two normal platelets are seen in the capillary lumen.

Courtesy of Helmut Rennke, MD.

Treatment

- Immunosuppressive therapy:
  - Steroids + cyclophosphamide
  - Azathioprine
  - Cyclosporine
  - Rituximab.