Glomerular diseases with organized deposits

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What is an organized deposit?

• A number of glomerular diseases accompanied by organized deposits

• Organized deposit = extracellular deposits organized into substructures: fibrils, hallow microtubules, curved microtubules, spheres, crystalloid structures, fingerprints

• Accurate diagnosis needs multiple pieces:
  • Clinical history and lab data; LM, IF, EM

• Observe whether there is increased mm (silver positive) or replaced mm with abnormal extracellular material (silver negative).
Renal diseases with organized deposits are relatively uncommon.

- **Amyloidosis**: 5-8% of renal biopsies
- **Fibrillar, immunotactoid and cryoglobulinemic GN**: at most 1% of all renal biopsy
- **Diabetic fibrillosis**: uncommon
- **Fibronectin and collagenofibrotic** glomerulopathy: extremely rare (few reported cases in the literature).

Mesangial expansion

Silver methenamine (-)

Congo red stain

- Electron microscopy
  Fibrils 10-15 nm
  IHC: strong mesangial fibronectin staining
  Fibronectin GP
  Lupus
  LHCDD

Silver methenamine (+)

Banded fibers-collagen

Glomerulosclerosis

IHC: Collagen III

EM: non-branching fibrils 8-12nm

Random fibrils 15-30nm

Microtubules

Amyloidosis

Granular glomerular IgG and C3

Parallel >30 (20-90nm)

Fibrillary GN

Immunotactoid GN

Curved and comma shaped with periodicity of 43 to 65 nm

Collagenofibrotic GP

IHC: strong mesangial fibronectin staining

Paired, curved 25-35nm

Cryoglobulinemic GP

Fibrils in bundle 10-20nm

Diabetic fibrillosis
Case # 1

• A 59 year old female patient
• Medical history: Pulmonary fibrosis, fibromyalgia and hepatitis C.
• Presented with nephrotic syndrome, hematuria and increase in her creatinine level from a baseline of 133 to 361 Umol/l (nl:50-105) over a period of one month.
• ANCA: 698 MFU (normal levels <120)
• dsDNA: negative
• Cryoglobulins: negative
What is your differential diagnosis?

1. MPGN
2. Membranous nephropathy
3. IgA nephropathy
4. Fibrillary GN
5. Lupus nephritis
6. Amyloidosis
Case # 1

- Diffuse crescentic [fibrillary glomerulonephritis](#)
- Cannot completely exclude a superimposed ANCA-associated injury.
- F/U: patient was treated with Prednisone and cyclophosphamide without amelioration of her renal function.
- Patient deceased after 2 months from pulmonary edema.
Fibrillary Glomerulonephritis:

- **Incidence:** <1% of native kidney biopsy.

- **Age:** Average 50-55 years, range from 19-81 years.

- **Ethnicity and Gender:** Caucasian predilection (>90%) with slight female predominance.
- Most cases are idiopathic. Some are associated with: malignancy (23%, mostly carcinoma), monoclonal gammopathy (17%), and autoimmune diseases (15%).

- **Clinical manifestations:** localized to the kidneys. Proteinuria with 38% in the nephrotic range, hematuria (52%) and hypertension (71%).

- **Outcomes:** Poor. 50% of patients progress to ESRD within 3 years of diagnosis.
- Can recur after renal transplantation (35-50%).

Fibrillary Glomerulonephritis:

- **LM:**
  - diffuse proliferative GN;
  - MPGN
  - Mesangioproliferative or expanded mesangial regions with acellular mat.
  - Membranous pattern
  - Crescents in 20% of cases (usually less than 20% of the glomeruli).

- **IF:**
  - granular or pseudolinear capillary loop and mesangial staining for IgG (IgG4 and IgG1 predominate)
  - C3 (92%), C1q(60%),
  - kappa and lambda (polyclonal, sometimes LC restriction, kappa)

- **Electron Microscopy:** randomly arranged, 10 to 30 nm diameter fibrils in the mesangium and peripheral capillary walls.
Immunotactoid Glomerulopathy

- **Incidence:** Occurs 1/10th as frequently as Fibrillary GN, <0.1% of native kidney biopsy.

- **Age:** Older population than fibrillary GN (mena age 62)

- **Ethnicity and gender:** Caucasian predilection with slight female predominance.

- **Clinical manifestations:** Nephrotic syndrome and hematuria, hypocomplementemia. Progression to ESKD occurs in a slower pace and not as often as fibrillary glomerulopathy.

- Monoclonal gammopathy in 63%, lymphoprolifertive disorders in most cases (67%) (CLL, MM, plasmacytosis). Therefore, these disorders should be R/O after the diagnosis of Immunotactoid GP.

- Recurrent disease after renal transplant has been reported (50%).

Alpers CE. JASN.19:34-37.2007
Nasr et al. NDT 2012
Immunotactoid Glomerulopathy

- **Light Microscopy:**
  - Varying degrees of mesangial expansion
  - MPGN, membranous pattern, proliferative
  - Nodular glomerulopathy

- **IF:** mesangial and peripheral capillary loops, IgG and C3 staining with granular pattern. Rare cases show IgM or IgA. Light chain restriction can be seen.

- **Electron Microscopy:** microtubular or cylindrical structure measuring more than 30 nm in diameter organized in parallel arrays in mesangium, can extend to peripheral loops. No granular ICs.

- In lupus nephritis, ICs may polymerize to form microtubular structures, however, also present granular ICs.
Immunotactoid GP
Cryoglobulinemic Nephropathy:

- Incidence: Occurs in 24% of patients with cryoglobulinemia and is characterized by remissions and exacerbations.
- Most frequent in females.
- Clinical manifestations: Nephrotic syndrome (75%), hematuria (100%), isolated proteinuria, purpura, arthralgia and other signs of vasculitis.
- Prognosis: Only a small percentage (10%) of patient progress to ESRD. The prognosis depends on the underlying lymphoproliferative disease.

Cryoglobulinemic Nephropathy:

- **Light Microscopy:**
  - Mild mesangial proliferation
  - Membranoproliferative GN with duplication of the GBM
  - Intracapillary pseudothrombi “hyaline thrombi”
  - Segmental necrosis
  - Vasculitis may be present

- **Immunofluorescence:** Variable. Granular capillary loop and mesangial deposits of IgG or IgM, LC restriction can be seen.

- **Electron Microscopy:**
  - Cryo deposits in subendothelial area or intracapillary hyaline thrombi.
  - Paired, curved, microtubular and or circular structures measuring 20-30nm.
  - Other appearances include fibrillar or amorphous deposits as well as some with fingerprints.
  - The curvilinear pattern is much more frequent in type II.
Cryoglobulinin structures by EM

Microtubular structure

Curved pattern
Fibronectin Glomerulopathy

• **Incidence:** Very rare autosomal dominant disease.

• **Age:** range from 14-64 years.

• **Clinical manifestations:** Proteinuria in the nephrotic range, microhematuria and hypertension.

• **Prognosis:** Progression to ESRD is variable and some patients progress slowly.
**Fibronectin Glomerulopathy**

- **Light Microscopy:** Glomeruli are enlarged with mesangial expansion without hypercellularity.
  - The fibronectin deposits are nonargyrophilic, red on MT and stain intensely with PAS.
  - The morphologic changes are limited to the glomeruli.

- **Immunofluorescence:** Weak granular mesangial deposits of IgG, IgM and C3.

- **Immunohistochemistry:** Strong mesangial positivity with fibronectin.

- **Electron Microscopy:** Mesangial and subendothelial electron dense deposits.
  - Amorphous deposits with focal filamentous structures measuring 9-16nm in diameter.
  - GBM are uninvolved.
Presence of randomly distributed fibrils of 10-25 nm in diameter. Decreased silver staining. The fibrils are restricted to the mesangium. No clinical significance. Ddx: amyloid, fibrillary GN
Collagenofibrotic Glomerulopathy:

• Incidence: Very rare autosomal recessive disease

• Age: All ages with usually onset of symptoms in early childhood or late adulthood.

• Ethnicity and gender: Japanese with no sex predelection.

• Clinical manifestations: Proteinuria, +/-nephrotic syndrome (60%), minor alteration in renal function, microhematuria and hypertension

• Lab data: Increase in serum pro-collagen III

• Prognosis: There is no treatment. Pace of progression is unpredictable. 35% of adults and 90% of children progress to ESKD.

Collagenofibrotic Glomerulopathy
Glomerulosclerosis:

- Is the final common pathway for irreversible glomerular injury.
- 3% of the sclerotic mesangium shows fibrillary structures creating diagnostic difficulties.
- These fibrils (precollagen) measure from 5-25nm. They lack the typical interstitial collagen periodicity of 65nm.
- Immunofluorescence: positive staining with IgM and C3.
- Should be differentiated from amyloidosis and fibrillary glomerulopathy.
Glomerulosclerosis

Parallel collagen fibrils, periodicity at 65nm
Take home messages

• Renal diseases with organized deposits are uncommon
• In many forms pathogenesis unclear
• Non-amyloid forms require EM for accurate diagnosis
• Immunotactoid glomerupathy diagnosis should trigger screening for lymphoproliferative disorders/hematological malignancies
• Detection of cryoglobulins difficult (test twice)
• Evidence for cryos (EM, lab test) – R/O HCV, SLE, monoclonal gammopathies, other infections, hematological malignancies
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http://www.sislaboratory.org/
Nail-Patella syndrome:

- Very rare hereditary disorder characterized by bone lesions, urinary tract abnormalities and renal involvement.
- The majority of patient have no apparent clinical manifestations.
- No treatment and 30% progress to ESKD at 33 years old with no risk of recurrence after transplantation.
- Light microscopy: -The glomeruli are unremarkable
  - Focal doubling of the GBM
  - Variable focal and segmental glomerulosclerosis.
- Immunofluorescence: negative
- Electron microscopy: moth-eaten appearance of the GBM. Presence of collagen fibrils in the lamina densa with parallel arrangement and characteristic periodicity (64nm).