Differential Diagnosis of Glomerular Diseases

Glomerulonephritis can be classified as: **Nephrotic or Nephritic (mild or moderate-to-severe)**

Nephrotic Syndrome

Proteinuria >3.5 g/day, Hypoalbuminemia, edema, hyperlipidemia + bland urinary sediment (few cells or casts)

Minimal change disease

- Most common cause of nephrotic syndrome in **children** (Children age <10)
- **Idiopathic** → T -cell injury to podocytes → increased permeability to albumin.
- **Associations** → **Hodgkin's lymphoma / NSAID**
- Children age <10 with isolated nephrotic syndrome do not require biopsy for diagnosis as MCD is highly likely → next step: **prednisone**.
  - LM: **Normal finding (MCQ).**
  - EM: **foot processes fusion of podocytes**
  - Immunofluoresence: negative.

Focal segmental glomerulosclerosis

- Most common cause of nephrotic syndrome in **adults.**
- **African American**
- **Associations** → **HIV / Heroin use / Obesity** (HHO)
  - LM: **focal and segmental glomerulosclerosis.**
  - EM: **foot processes fusion of podocytes**.
- Other forms of **HIV-related glomerulopathies** that can present with nephrotic-range proteinuria (less common than FSGN) :
  1. **Membranous glomerulonephritis** → if they also have hepatitis-B infection.
  2. **Membranoproliferative glomerulonephritis** → see below.
  3. **Diffuse proliferative glomerulonephritis** →In lupus nephritis type IV

Membranous nephropathy

- It is a common cause of nephrotic syndrome in adults + adolescents (14 yrs) especially if associated with HBV infection ***"hepatitis B virus-associated membranous nephropathy (HBVMN)"***
- **Associations** → **Adenocarcinoma (lung & breast) /Hepatitis B/ SLE/ NSAID** (ABSD)
  1. ***HBVMN :*** *serum C3 is low.*
  2. ***Lupus nephritis:*** *antinuclear antibody is elevated*
  - LM: **Thickened GBM and subepithelial "spikes".**
  - EM: **Subepithelial deposits.**
  - Immunofluoresence: **Granular IgG, C3.**

Membranoproliferative glomerulonephritis

- Membranoproliferative glomerulonephritis can be **Nephrotic** or **Nephritic**.
- **Associations** →**Hepatitis B** *(less common than membranous nephropathy)*
  Hepatitis C → **mixed cryoglobulinemia** ***(test for viral markers)*** :
  - The immune complexes are IgM antibodies (similar to RF) that form complexes with IgG anti-hepatitis C virus antibodies → Immune complex deposition in small blood **vessels (vasculitis).**
    - Skin (eg, palpable purpura doesn't blanch with pressure)
    - **Kidney (eg, MPGN)**
    - Nervous system (eg, motor sensory axonopathy),
    - Musculoskeletal system (eg, arthralgias).
  - Serologically (**serum cryoglobulins** + **low complement levels** + **increased RF + increased liver enzymes**) + Biopsy.

D.D. of Low complement levels with glomerulonephritis	
Postinfectious GN	Occurs 10-21 days after a streptococcal or staphylococcal infection.
Lupus nephritis	Positive **antinuclear antibody**.
Mixed cryoglobulinemia with hepatitis C	Positive HCV + increased RF

  - LM: **Mesangial hypercellularity**
  - EM: Type I: **Mesangial and subendothelial deposits.**
    Type II: **Dense deposits Disease (DDD) in GBM**
  - Immunofluoresence: **Granular IgG, C3 (in type I)**

Diabetic Nephropathy

Diabetes mellitus is the leading cause of end-stage renal disease in United States

- Patient with diabetes for long time (> 10 years) + poor glycemic control.
- Diabetic nephropathy is characterized by **proteinuria** & progressive decline in GFR.
- ***Glomerular hyperfiltration (MCQ)*** is **the earliest renal abnormality** seen.
- **Histology :**
  - First change that quantitated: ***Thickening of the glomerular basement*** **membrane**.
  - Pathognomonic hallmark: **nodular glomerulosclerosis (Kimmelstiei-Wilson nodules).**
  - The most common histologic lesion is ***diffuse glomerulosclerosis***

Amyloidosis

- ***Rheumatoid arthritis*** *is the most common cause of AA amyloidosis in the United States.*

- Amyloidosis is a group of dieases in which amyloid fibrils, builds up in tissue.
- Deposits consist of **light chains (AL amyloidosis)** or **abnormal proteins (AA amyloidosis).**

	AL amyloidosis	AA amyloidosis (Inflammatory amyloidosis)
Associated condition	• **Multiple myeloma** • Waldenstrom Macroglobulinemia	**Chronic inflammatory conditions:** • **Rheumatoid arthritis** • **Inflammatory bowel disease**
Composition of amyloid	• **Light chains** (usually lambda).	**Abnormally folded proteins:** beta-2 microglobulin, apolipoprotein or transthyretin

- **History:**
  - Patient with ***Rheumatoid arthritis***, presented with **nephrotic manifestations** +
  - **Hepatomegaly**. + U/S : **bilateral kidneys enlargement.**
- **Renal biopsy:**
  - Amyloid deposits are seen in GBM, blood vessels, and interstitium of the kidneys.
  - Immunofluoresence: **Deposits that stain with Congo red** and demonstrate a characteristic **apple-green birefringence under polarized light.**
  - EM: randomly arranged **thin fibrils.**

Nephritic Syndrome

RBCs (dysmorphic), WBCs, casts (red blood cell and/or white blood cell), and variable degrees of proteinuria

IgA nephropathy (Berger's disease)

- IgA nephropathy can present with nephrotic syndrome (<10%), but more commonly (40%) presents with hematuria following an URT infection.
- **Associations** → **Upper respiratory tract infection (within 5 days)**
- **Symptoms :**
  - More common in young adult men (age 20-30)
  - Presents as: ***episodes of gross hematuria***
- **Diagnosis :**
  - **Serum complements: Normal**
  - **Kidney biopsy: Mesangial IgA deposits seen in**

Poststreptococcal Glomerulonephritis

- Acute post-streptococcal glomerulonephritis after throat or skin infections with B-hemolytic streptococcal infection.
- **Associations** → **Upper respiratory tract infection (10-21 days postpharyngitic)**
- **Symptoms :**
  - More common in children (age 6-1 0), but can occur in adults.
  - Presents as: gross **hematuria**.
- **Diagnosis :**
  - **Serum complements: Low**
  - **Kidney biopsy: subepithelial humps consisting ofC3 complement.**
  - ***Elevated anti-streptolysin O &/or anti-DNAse B***

Lupus nephritis

- Immune complexes composed of **dsDNA (and) anti-dsDNA antibodies** deposit in :
  1) **Mesangium and/or subendothelial space** → inflammatory reaction with activation of complement system, lowering C3 & C4 (***Diffuse membranoproliferative GN).***
  2) **Subepithelial space** → presenting with **nephrotic syndrome** without normal complement levels ***(membranous GN)***
- **Laboratory :**
  - Anemia, leukopenia, thrombocytopenia
  - Positive ANA, anti-dsDNA, anti-Sm
  - Low complement levels, increased immune complexes