## PATHOLOGY OF GLOMERULAR DISEASES

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Pathophysiology and Clinical Presentation</th>
<th>Lab Findings and Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Urinalysis in Nephrotic Syndrome | NML excretion: 150 mg/d  
< 0.15 g total protein/g urine creatinine  
Nephrosis: > 3.5 g/d OR > 3.5 g/g urine creatinine  
Lipiduria and fatty casts (Maltese cross appearance when illuminated by polarized light)  
2+/3+ on dipstick without microhematuria | Presents with the classic tetrad of nephrotic syndrome  
Massive proteinuria (>3.5 g/d)  
Hypoalbuminemia  
Edema  
Hyperlipidemia | LM: no changes  
IF: no changes  
EM: podocyte foot process effacement  
Bx is usually not necessary | Prednisone  
Usually controls disease if onset and treatment is early in life  
With age, recurrence is more likely |
| MINIMAL CHANGE NPHROTIC SYNDROME | Typically a pediatric disease  
Loss of anionic epithelial layer (podocyte processes) of the filtration barrier  
Typically diffuse and global |                                                                                                              |                                                                                           |                                |
| FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) | Inherited  
Mutations in the Nephrin gene product result in dysfunctional slit diaphragms (Finnish Congenital Nephritic Syndrome)  
Infective  
HIV infection (collapsing glomerulopathy)  
Loss of Renal Mass  
Unilateral renal agenesis  
SCD  
Vesicoureteral Reflux  
Some evidence for circulating toxins, since Dz recurs after transplantation | Nephrotic Syndrome  
Results in progressive kidney failure  
Can be thought of as a more severe variant of MCNS  
The primary injury is podocyte foot process obliteration | LM: focal segmental fibroplasia and obliteration of the capillary lumen + hyaline deposits  
EM: widespread effacement of foot processes  
IF: Minimal IgM and C3 deposits; no immune complexes | Transplantation  
ACE inhibitors  
Prednisone |
<table>
<thead>
<tr>
<th><strong>MEMBRANOUS GLOMERULOPATHY</strong></th>
<th>Autoimmune Depression of immune complexes in the subepithelial space IgG and complement form complexes with cryptic GBM antigens + allergens, pathogens, and drugs</th>
<th>Nephrotic Syndrome Results in renal failure with increasing serum BUN and creatinine</th>
<th>LM: thickening of the GBM with spiking into the urinary space IF: granular deposits (immune complexes, IgG, C3) along the GBM</th>
<th>ACE inhibitors Predisone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIABETIC NEPHROPATHY</strong></td>
<td>A frequent sequela of DMI and DMII Glycosylation of surface proteins → conformational changes → hyperfiltration The disease is exacerbated by systemic hypertension</td>
<td>Microalbuminuria progressing to nephrotic syndrome and renal failure NML urinary albumin: &lt; 30 mg/g creatinine Microalbuminemia: 30 – 300 mg/g creatinine <em>These ranges are not detectable by dipstick</em></td>
<td>LM: diffuse nodular mesangial matrix expansion (Kimmelstiel-Wilson Nodules) + capillary thickening + hyaline casts in efferent and afferent arterioles IF: Linear deposition of IgG and albumin is due to greatly increased endothelial permeability</td>
<td>ACE inhibitors ARBs Dual kidney and pancreas transplantation in ESRD</td>
</tr>
<tr>
<td><strong>AMYLOIDOSIS</strong></td>
<td>Deposition of Immunoglobulin Light chain infiltration secondary to multiple myeloma AL amyloidosis Chronic Inflammation Deposition of Protein AA secondary to RA and chronic osteomyelitis</td>
<td>Proteinuria in nephrotic range Systemic disease Progresses to ESRD</td>
<td>LM: stain with CR and illumination with polarized light reveals green birefringence. Deposits are typically amorphous and eosinophilic. EM: Fibrillar deposits</td>
<td></td>
</tr>
<tr>
<td><strong>SECONDARY HYPERTENSION</strong></td>
<td><strong>HYPERTENSIVE NEPHROSCLEROSIS</strong> Culpable for 25 – 40% of all ESRD Sequela of longstanding HTN Vascular injury → atherosclerosis of large vessels + arteriolosclerosis of smaller vessels → ischemia and necrosis of renal parenchyma</td>
<td>Gross: Nodular and fibrosed surface; loss of parenchymal volume; cortical denuding, fibrosed renal pyramids LM: intimal proliferation, hyperplasia of tunica media, reduplication of elastic lamina, luminal obliteration Glomerular sclerosis, hypertrophy of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALIGNANT HYPERTENSION</td>
<td>Severe HTN</td>
<td>Typically requires DBP &gt; 130 mmHg</td>
<td>The disease is systemic</td>
<td>the medial SM</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------</td>
<td>-----------------------------------</td>
<td>-------------------------</td>
<td>--------------</td>
</tr>
</tbody>
</table>

**NEPHRITIC SYNDROME**

**Urinalysis in Nephritic Syndrome**
- Active urine sediment (dysmorphic RBCs + RBC casts)
- Hematuria on dipstick (measures heme; thus can be elevated with muscle damage and intravascular hemolysis)

**Characteristics of Nephritic Syndrome:** discolored (darkened) urine, HTN, AKI with oliguria

**IMMUNOGLOBULIN A NEPHROPATHY (BERGER DISEASE)**
- Most common primary glomerular disease
- Usually correlated with URIs and other bacterial infections
- Striking presentation: visible hematuria following soon after respiratory infection (typically 1 - 3 d).
- Typical presentation is hematuria and subnephrotic proteinuria
- May convert to nephrotic syndrome
- Dx requires Bx + r/o infection
- LM: hypercellularity of the mesangium
- EM: electron-dense deposits within mesangium
- IF: detection of IgA deposition within the mesangium
- May progress to renal failure: requires dialysis or transplant

**ANTI-GBM DISEASE (RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS)**
- These are diseases with rapid progression to renal failure
- **Autoimmune Mechanism**
  - Circulating Abs against Type IV collagen within the GMB → binding → elicit Type II hypersensitivity → activation of complement + cytokine release + plasma clotting cascade → glomerular damage and *sclerosis* → renal failure
  - The presentation is hematuria progressing to acute renal failure
  - Rapid rise in serum BUN and creatinine
  - **Goodpasture Syndrome**
    - Circulating antibodies are avid against GBM and the pulmonary basal laminae
    - Presentation is hematuria + hemoptysis
  - LM: focal capillary necrosis, crescentic masses within Bowman’s space (parietal epithelium + macrophages + fibrin)
  - IF: linear deposits of IgG
  - EM: NO electron-dense deposits
  - Serum: Anti-GMB Ab (this is diagnostic)
  - Immunosuppression
  - Plasmapheresis
  - Response occurs only if Tx is initiated early.
  - Transplant after decline in Anti-GMB titre.

**THIN BASEMENT MEMBRANE NEPHROPATHY (BENIGN FAMILIAL HEMATURIA)**
- Inherited
- AD pattern
- Prevalence ~ 10%; typically asymptomatic
- ECF volume is NML
- Renal function is typically NML
- Presentation is microhematuria wth a relatively benign course
- LM: NML glomerular morphology
- EM: thinned GBM
- Dx: FH + clinical Hx + Bx
| ALPORT SYNDROME | Mutations involve the Collagen IV gene.  
Alport demonstrates X-linked inheritance | Microhematuria **progressing** to renal failure  
Extrarenal pathology: sensorineural hearing loss, cataracts, lens dislocation | EM: thickened, split, and laminated GBM  
Dx: FH + clinical Hx + Bx |
| --- | --- | --- | --- |
| LUPUS NEPHRITIS | **Immune Complexes**  
ANA + DNA complexes are deposited throughout the glomerulus (subepithelial, subendothelial, mesangial) → activation of complement | Renal involvement of SLE ranges from microhematuria to nephrotic syndrome  
A common finding in advanced disease is hematuria + nephrotic syndrome  
There are six clinical stages of LN  
1. Minimal Mesangial  
2. Mesangial Proliferative  
3. Focal Lupus Nephritis  
4. Diffuse Lupus Nephritis  
5. Membranous Changes  
6. Advanced Sclerosing Nephritis  
Most patients present in Stage IV  
Note that renal disease occurs within the clinical spectrum of SLE:  
Malar rash, hematologic abnormalities (anemia, leucopenia), serositis, neurologic deficits, arthralgia, complement depletion, elevated ESR | LM: diffuse proliferation of all cell types, capillary thickening into wire-loop lesions (immune complex deposits), hypercellular mesangium, increased mesangial matrix  
IF: IgG, IgA, IgM + complement (C3, C4, C1q) in granular pattern  
Full-House staining!  
EM: electron-dense deposits in mesangium, **subendothelium**, and GMB; tuboreticular inclusions (microtubule concretion formed in a background of IFN-γ)  
Serum: ANA, anti-dsDNA Ab  
Prednisone  
Cyclophosphamide  
Mycophenolate Mofetil |
| MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN) | **Immune Complexes**  
Idiopathic MPGN (Types I – III)  
Autoimmune Dx: SLE, RA, Sjogren’s  
Chronic Infection: HepC with cryoglobulins, HepB, endocarditis, malaria, schistosomiasis  
**Resolving Thrombotic Microangiopathy**  
Convalescent HUS or TTP  
Antiphospholipid Antibody Syndrome  
Dense Deposit Disease | Hematuria + Nephrotic Syndrome  
(Similar to Lupus Nephritis)  
NH: gradual decline in renal function with progression to ESRD within 10 yrs in 50% of patients | LM: large and lobular glomeruli with increased cellularity, split capillary walls (tram-track appearance) due to interposed mesangium  
IF: C3 without immunoglobulin. GBM may be replaced with continuous electron-dense deposits  
**Dense Deposit Disease (MPGN Type II)**  
EM: hypercellular mesangium, menangial interposition into the GBM, split GBM, **subendothelial** and **GBM**  
Steroids and immunoisuppression NOT EFFECTIVE  
Recurrs after kidney transplant |
### POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

**Infection with Nephritogenic Group A Streptococci**
- Typically seen only in developing countries
- Inflammation can occur via two mechanisms
  - Bacterial nephritis-associated streptococcal plasmin receptor (NAP1r) → binds to glomerular subepithelium → local inflammation
  - Circulating immune complexes (M protein:IgG or serine proteinase:IgG) → deposit into subepithelium → activation of complement

- **Manifest approximately 10 d. following streptococcal pharyngitis**

- **Edema**
- **Hematuria**
- **Hypertension**

- **LM:** enlarged glomerular tufts, endothelial proliferation, PMN infiltrates
- **IF:** granular deposits of IgG (complexed to Strep Ags) and C3
- **EM:** semilunar densities located in the subepithelium

- **Serum:** ASO +ve, depleted C3 (involved in classical pathway of Ab binding)

- **Tx edema and HTN**
- **Prophylaxis with ABx**

### VASCULITIS

**PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS**
- Wegner’s Granulomatosis
- Microscopic Polyangiitis
- Churg-Strauss Syndrome

**Renal Arteries** are affected in **Polyarteritis Nodosa**
- Viral infection or cytokine release → expression of intracellular protein on neutrophil plasmalemma (Proteinase 3 or myeloperoxidase) → reaction with circulating ANCA → degranulation and tissue injury

- **These diseases are typically systemic (except renal-specific MPA)**
- Thus, a Pulmonary-Renal syndrome is typically seen
- It is not mediated by immune complex deposition!
- **NH:** diseases are typically classified as RPGN, along with anti-GBM disease

- **Wegener’s Granulomatosis**
  - LM: Focal necrosis of glomerular capillaries, cellular crescents in Bowman’s space, renal and pulmonary granulomas
  - Serum: cANCA against Proteinase 3
  - IF: diffuse granular signal (cANCA), fibrin, NO immunoglobulin or complement
  - EM: no protein deposits

- **Microscopic Polyangiitis**
  - LM: focal capillary necrosis, glomerular crescents
  - IF: perinuclear enhancement of granular deposits within neutrophils (pANCA), fibrin, NO immunoglobulin or complement
  - EM: no protein deposits

- **Prednisone**
- **Cyclophosphamide**
- **Mycophenolate Mofetil**

- **Treatment must be initiated early in the disease history**
<table>
<thead>
<tr>
<th>THROMBOTIC MICROANGIOPATHY</th>
<th>Pediatric Hemolytic Uremia Syndrome (HUS)</th>
<th>Endovascular injury → loss of thromboresistance → platelet activation → fibrin deposition → formation of microthrombi</th>
<th>LM: extensive deposition of fibrin in glomerular capillaries and larger renal vessels, endothelial swelling and proliferation, fibrin thrombi IF: fibrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravasation of EHEC or Shigella toxin → renal intravascular coagulation → renal failure</td>
<td></td>
<td>The clinical presentation is Hematuria Microangiopathic Hemolytic Anemia Intravascular RBC fragmentation seen on peripheral blood smear Thrombocytopenia (diathesis) Rapidly progressive renal failure (uremia)</td>
<td></td>
</tr>
<tr>
<td><strong>Adult HUS</strong> (without GI illness) May be secondary to BLEO, cisplatin, and cyclosporine Antiphospholipid Antibody Syndrome Scleroderma Complication of pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Familial HUS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic Thrombocytopenic Purpura (TTP) Defective vWF cleaving protease → oligomerization of vWF → hypercoagulability → platelet activation → microthrombi May also be caused by a cryptic circulating immunoglobulin → inhibit vWF protease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TTP: TX with plasmaphoresis + antiplatelet therapy</td>
</tr>
</tbody>
</table>