

Glomerulonephritis (nephritic syndrome)—inflammatory rupture of the glomerular capillaries with resultant bleeding into the urinary space; proteinuria and edema *may* be present but are usually mild.

Clinical findings:

- Oliguria
- Azotemia
- Hypertension
- Hematuria—results from leakage of RBCs directly from glomerular capillaries into Bowman’s space. Many RBCs are aggregated into the tubules and embedded into a proteinaceous matrix→red cell casts in urine→smoky brown urine; may degenerate into pigmented granular casts.

Glomerular inflammation→decreased GFR→azotemia

→renin release→Na, H₂O retention→edema
→HTN

Normal RBCs in urine up to 1,000,000

Hematuria may also come from other sources in urinary tract (infection, stone, cancer)
“glomerular hematuria”—dysmorphic RBCs, RBC casts, or significant associated proteinuria

Glomerulonephritis versus Glomerulopathy

Glomerulonephritis:

deposition of immune complexes → inflammation

Assoc with nephritic syndrome

i=inflammation

- Hematuria
- Oliguria
- Azotemia
- Hypertension
- RBC casts
- Proteinuria (less severe)

Glomerulopathy:

signs of glomerular disease, no inflammation

Assoc with nephrotic syndrome

o= proteinuria

- massive proteinuria
- generalized edema
- low serum albumin
- fatty casts

Diseases causing Nephrotic Syndrome:

1. Minimal change (lipoid) disease:
 - most common cause of nephrotic syndrome in kids
 - usually present after URI, commonly in boys
 - Micro & IF: normal
 - EM: fusion of foot processes
 - RESPOND WELL TO STEROIDS
2. Membranous GN: most often idiopathic, can be assoc with systemic disease (SLE, cancer, others)
 - Most common cause of nephrotic syndrome in adults
 - Most patients > 30 years
 - Micro: thickening of the BM, no cellular proliferation
 - IF & EM: granular IgG, subepithelial deposits, “spike and dome” appearance
3. Membranoproliferative GN: occurs as Type 1 or 2 (overall most cases are type 1): both have thickening of BM & cellular proliferation, occurs in ages 5-30
 - TYPE I - Immune complex disease, strong assoc with Hep C, see tram-tracks in glomeruli
 - IF: granular all Igs & complement
 - EM: subendothelial deposits
 - TYPE 2 - anti-C3 antibody (nephritic factor)
 - IF: granular C3
 - EM: intramembranous deposits
4. Focal segmental glomerulosclerosis: spectrum of disease, assoc with HIV (worse disease), no immune complex deposition
 - involve only some glomeruli with hyalinization, no visible BM changes.
 - poor prognosis, does not respond well to Rx

5. Diabetic glomerulosclerosis
 - overall most common cause of end-stage renal disease
 - *Basement membrane markedly thickened*, diffuse or nodular mesangial accumulations of basement membrane-like material.
 - Increase in mesangial matrix, resulting in two characteristic appearances:
 - a. Diffuse glomerulosclerosis—diffusely distributed increase in mesangial matrix
 - b. Nodular glomerulosclerosis—nodular accumulations of matrix (Kimmelstiel-Wilson disease)
6. Amyloidosis: manifestation of systemic amyloidosis (also rheumatoid arthritis, multiple myeloma)
 - deposition of amorphous pink material, positive with Congo red stain
 - subendothelial and mesangial amyloid deposits

Glomerulonephritis:

1. Post-strep glomerulonephritis
 - Viral protein→immune complex formation→deposition in glomeruli→complement activation→glomerular damage
 - mostly kids, present 2-4 wks after a strep throat infection
 - have short-lived nephritis syndrome, see periorbital edema & generalized edema
 - most pts recover without sequellae, very small minority develop RPGN
 - micro:hypercellular glomeruli with mesangial & endothelial cells (see polys, lymphs)
 - EM: subepithelial immune complexes (isolated humps)
 - IF: “lumpy bumpy” (very coarse granular IF for C3 and IgG)
 - ASO (antistreptolysin Ab), anti-DNAse B, decreased serum C3
2. Rapidly progressive glomerulonephritis (RPGN)
 - Nephritic syndrome→renal failure within weeks-months
 - Formation of crescents between Bowman’s capsule and glomerular tuft, represents fibrin deposition and proliferation of cells in Bowman’s space. Crescents=BAD
 - 50% of cases with immune complexes are post-strep; other immune complexes as in lupus and IgA nephropathy. RPGN Type II
 - Antiglomerular BM Ab in 10% (Goodpasture). RPGN Type I
 - May also be pauci-immune type—no immune complexes. This type often associated with ANCA. RPGN Type III
3. Goodpasture Syndrome (antiglomerular basement membrane disease)
 - Ab to basement membrane, directed against antigens in pulmonary and glomerular basement membranes
 - Nephritic syndrome, hemoptysis, men in mid-20s
 - EM: RPGN crescentic morphology
 - IF: Linear immunofluorescence against IgG
 - Stain for anti-GBM Ab
4. Alport Syndrome
 - Hereditary nephritis, males, associated with nerve deafness, ocular disorders
 - Isolated hematuria, not necessarily nephritic syndrome, ESRD by 30

- Alpha-5 chain type of Type IV collagen mutation
- GBM thickening with splitting of lamina densa
- EM: irregular thickened GBM

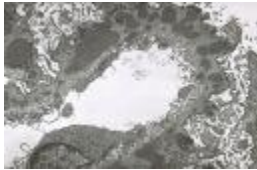
“Other” Glomerular Diseases

1. IgA nephropathy (Berger disease)
 - Overall most common form of GN
 - Can present in child or adult
 - Most commonly, benign recurrent hematuria in children, usually following infection, lasts 1-2 days, may be component of Henoch-Schonlein purpura (HSP)
 - micro & EM & IF: focal mesangial deposits, positive for IgA
 - do not respond to steroids or immunosuppression
2. Membranoproliferative Glomerulonephritis (MPGN)
 - Clinically slow progression to chronic renal disease
 - See nephrotic or nephritic presentation
 - Both BM thickening and cellular proliferation of mesangial matrix
 - Reduplication of GBM→2 layers; due to expansion of mesangial matrix into glomerular capillary loops, leads to *tram-track appearance*, best seen with silver stains
 - **Type I**—immune-complex nephritis, assoc with unknown antigen. Striking tram-track
 - **Type II**—aka dense deposit disease. Irregular electron-dense material deposited into GBM; C3 adjacent to but not within dense deposits. Serum C3 markedly reduced. Possible caused by IgG autoAb—C3 nephritic factor
3. Thin GBM Disease
 - Genetic defects in alpha-3 chain of collagen Type IV→thin GBM→more subject to damage
 - EM: Thin GBM
 - Familial, asymptomatic hematuria, good prognosis

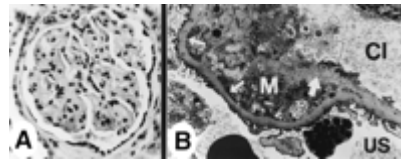
Immune Injury, Microscopy

- IF, EM can establish presence, type of immune complexes
- LM in glomerular disease:
 - Focal= <50% of glomeruli involved
 - Diffuse= >50% of glomeruli involved
 - Global= all glomeruli involved
 - Segmental= portion of individual glomerulus involved
- Glomerulonephritis=inflammation in glomerulus
- Types of injury:
 - Acute/active—accumulation of inflammatory cells, necrosis, neutrophil or fibrin exudates
 - Chronic/persistent—cellular proliferation→abnormal excess GBM, mononuclear hypercellularity (mesangial proliferation)
 - Repair of injury→fibrosis, scarring, sclerosis

- Location of process:
 - Mesangial—confined to mesangium with capillary loops easily defined, intact
 - Endocapillary—within GBM in glomerular tuft
 - Extracapillary—Bowman’s space, e.g. crescent formation
- Excess collagen production in response to injury:
 - Membranous—thickening of GBM in peripheral capillary loop; used exclusively in reference to thickening due to subepithelial immune complex deposition (deposition on podocyte side of membrane). Associated with production of excess GBM material between immune complexes, seen as spikes on silver stain
 - Mesangiocapillary pattern—widening of capillary loop, expansion of mesangium. Interchangeable with membranoproliferative GN, reaction to deposition of immune complexes in mesangial and endothelial side of peripheral loop GBM. Gives double contour/tram track appearance.



membranous



mesangiocapillary (membranoproliferative)

- Immunofluorescence
 - Detect presence of Ig and complement
 - Highlight areas with abnormal accumulations
 - Linear contour—Anti-GBM antibodies—follow contour of GBM, smooth
 - Granular IF—lumpy-bumpy, characteristic of circulating immune complexes.
 - In-situ complexes—antibodies directed against intrinsic fixed antigens that are normal components of GBM, linear IF
 - Circulating complexes—glomerular injury caused by trapped Ab-Ag complexes within glomerulus. Ag-Ab complexes have no specificity for glomerular constituents; just get trapped due to nature of glomerulus. Complement binds and causes damage. Clumps form in mesangium, or between endothelial cells and GBM (subendothelial), rarely between podocytes and GBM (subepithelial). If rapid course (post-strep GN), complexes degraded and symptoms subside; if chronic (HCV, HBV, SLE), repeated injury and more membranoproliferative pattern.
- Electron microscopy
 - Can see immune complex deposition (subepithelial or subendothelial)
 - Can see amyloid
 - Can see intramembranous deposits (e.g. dense deposit disease)
 - GBM lesions (Alport)
 - Podocyte foot process fusion

- Serology
 - ANA (SLE, connective tissue diseases)
 - ANCA (vasculitis—Wegener's, microscopic polyangitis)
 - Anti-GBM antibodies (Goodpasture)
 - ASO, Anti-DNAse (Strep GN)
 - HBV, HCV Ab and Ag
 - Complement (C3, C4)—decreased serum complement in immune complex GN, e.g. postinfectious GN, SLE, MPGN. Does *not* occur in IgA nephropathy, or membranous glomerulopathy
 - C3 nephritic factor—dense deposit disease
 - Anti-phospholipid Ab—SLE

Lupus Nephropathy

- Severity of renal lesions often determine overall prognosis in a lupus patient
- Often manifests as nephrotic syndrome, may have nephritic component
- WHO divides into 5 classic patterns
 - Type I—No renal involvement
 - Type II—mesangial form. Focal and segmental glomerular involvement, increase in mesangial cells and mesangial matrix. Slight proteinuria, minor hematuria, little consequence
 - Type III—Focal proliferative form. Less than 50% of glomeruli, but may cause severe damage to individual glomeruli
 - Type IV—Diffuse proliferative form. Most severe form, often associated with nephrotic and nephritic syndromes. Involves almost all glomeruli, marked inflammation, focal thromboses and mesangial proliferation→severe scarring. Wire loop abnormality from immune complex deposition and thickened GBM. Endothelial cell proliferation, subendothelial immune complex deposition
 - Type V—membranous form. Indistinguishable from primary membranous GN.

Tubular Disorders of the Kidney

- Characterized by abnormalities of solute transport

Tubular Diseases

- Fanconi syndrome—generalized loss of proximal tubule function→glycosuria, aminoaciduria, phosphaturia, uricosuria, proximal renal tubular acidosis
- Renal tubular acidosis (RTA)
 - Type I—inadequate proton secretion in distal nephron
 - Type II—Defective HCO₃ reabsorption in proximal tubule
 - Type IV—Impaired aldosterone effect→hyperkalemia and acidosis

Tubular injury

- Defective urinary concentrating ability→nocturia, polyuria
- May present as acute renal failure (especially acute tubular necrosis (ATN))
- Acute tubular injury—raggedness of epithelial lining, sloughing of cells, coagulative necrosis. Tubules do not ordinarily proliferate, but can regenerate completely if stimulated by injury and tubular basement membrane is intact.

- Chronic injury—tubular atrophy and fibrosis, may have hypertrophy in residual tubules.
- Acute Tubular Necrosis
 - Most common cause of ARF
 - Is reversible—necrotic tubules will be replaced by new tubules in about 2 weeks, with complete return to normal function if patient placed on dialysis. But may be fatal if ignored.
 - Initial phase—slight decline in UO, slight rise in BUN
 - Maintenance phase—oliguria, may cause hyperkalemia and cardiac arrest. Rising BUN, metabolic acidosis. Need dialysis here.
 - Recovery phase—polyuria as tubules recover, hypokalemia becomes a problem.
 - Most frequently caused by renal ischemia, d/t prolonged hypotension or shock. Also myoglobinuria from crush injuries, gentamycin, ethylene glycol (antifreeze).
 - See pigmented granular and eosinophilic hyaline casts. “Muddy brown casts”
 - How do you tell what’s causing oliguria?
 - Prerenal—FeNa <1%
 - ATN—FeNa >2%