ACUTE GLOMERULONEPHRITIS
MAKING SENSE OF THE NOMENCLATURE

CLINICAL DEFINITION: acute nephritic syndrome, variable in presentation
- acute onset of hypertension (60%), edema (85%), oliguria (50%), hematuria (30%), back pain (5%) and non-specific complaints of malaise, nausea and vomiting.
- urinalysis reveals hematuria, mild proteinuria, red blood cell casts, dysmorphic red cells, wbc casts (maybe seen with exudative phase of GN), labs reveal elevated creatinine (>2 in 25% patients)

PATHOLOGIC CORRELATION: variable inflammatory cellular infiltration and cellular (mesangial, endothelial) proliferation, severity depends on extent of total glomeruli involved (diffuse >50%, focal <50 %), crescent formation, capillary obstruction.
- Light microscopy reveals severity and location of cellular infiltration and proliferation.
- Immunofluorescence reveals patterns immunoglobulin and compliment deposition.
- Electron microscopy reveals location of electron dense deposits of immunoglobulin.

PATHOPHYSIOLOGIC MECHANISM OF DESTRUCTION: diverse insults can initiate an immune attack against the glomeruli, usually towards the endothelial or subendothelial sites.
- **Immune complex** depositions: immune complexes are formed either directly at the glomeruli by binding of circulating antibody to foreign antigen that has become trapped in glomerulus or autoantigen that is part of glomerulus or they may be formed in circulation and then become trapped in glomerulus. This activates the compliment cascade and initiates the inflammatory process.
- **Pauci immune**: small vessel necrotizing vasculitis without significant immune complex deposition occurs possibly via ANCA mediated direct activation of neutrophil and monocytes leading to endovascular inflammation
- **Anti-GBM antibody**: antibody to a segment on Type IV collagen found in GBM and in some cases, pulmonary BM.

ETIOLOGIC CONSIDERATIONS

**Immune complex (70%)-low compliment**

- **Post-infectious GN** (usually due to GAS)
  - Epidemiology: males>females, children> adults, associated with pharyngitis in temperate climates and skin infections in tropic climates.
  - Clinical presentation: acute nephritic syndrome, within 1-6 weeks of initial pharyngeal or skin infection, natural history lasts 4-7 days.
  - Pathology: diffuse cellular infiltration of monocytes, lymphocytes, neutrophils and eosinophils in capillary lumen with endothelial and mesangial cell proliferation; IF reveals IgG and C3 deposition in granular pattern along mesangium and capillary walls, EM with subepithelial deposits of Ig.
  - Diagnostic tests: compliments (decreased C3 in 90 % cases, normal C4), antibodies to streptococcal antigens (ASO, antiDNAse B are positive in 85% cases due to skin infection and 95 % cases due to pharyngitis); cryos (type III may be positive).
  - Prognosis: very good, 0.5 % mortality within acute disease, <2% progress to RPGN
  - Treatment: supportive therapy with diuretics and ACE inhibitors, steroids only if evidence of crescents on biopsy, treat strep infection.

- **Bacterial endocarditis GN (associated with SBE of S. viridans, acute BE of S. aureus)**
  - Epidemiology: 25% prevalence in post-mortem SBE cases, 40 % cases on ABE
  - Pathology: diffuse neutrophil and monocyte infiltration with mesangial and endothelial proliferation; granular deposition of IgG, IgM and C3 in mesangium and capillary walls, EM with subepithelial deposits of Ig.
  - Diagnostic tests: compliments (decreased C3 & C4 in 70-90 % cases), blood cultures, echocardiogram, cryos (type III may be positive).
  - Prognosis and treatment: must eradicate infection with antibiotics and valve replacement.

- **Cryoglobulinemic GN: associated with HCV infection**
• Clinical presentation: syndrome of purpura, weakness and arthralgias, 20-30% patients with acute nephritic syndrome, 20% with nephrotic syndrome, 50% mild proteinuria/hematuria.

• Pathology: massive endocapillary infiltration of lymphocytes and monocytes with intraluminal thrombi, PAS-positive and Congo red negative, thickened glomerular basement membrane; IF reveals diffuse granular deposits of either IgG/IgM intraluminal and subendothelial along peripheral loops; EM reveals subendothelial deposits of fibrillar material.

• Diagnostic tests: complements (decreased C4, CH50, normal C3), positive cryoglobulins type II (polyclonal IgG, monoclonal IgM).

• Prognosis: 10% complete remission, 20% recurrent flares, 30% indolent CRI, 40% progress to ESRD; death usually due to other organ involvement.

• Treatment: effects of IFN and ribavarin on renal disease are controversial; steroid, cyclophosphamide, plasmapheresis have been used, data controversial.

• **SLE GN** (5 classes: normal, mesangial, focal proliferative, *diffuse proliferative*, membranous)

• Epidemiology: no non-renal SLE manifestation predicts likelihood of developing lupus nephritis; maybe be associated with black race, younger age and male sex.

• Clinical presentation: usually develops within first 5 years of diagnosis, 5% presenting feature in diagnosis, rarely develops after 5 years, 40% of patients with SLE and renal disease have acute nephritic syndrome.

• Pathology: depends n class; in DPGN, there is diffuse cellular infiltration and proliferation, basement membrane thickening. IF reveals IgG, IgM, IgA and C3 deposition, EM confirms deposits in mesangium, subendothelial and subepithelial (this is most aggressive lesion).

• Diagnostic tests: ANA (positive >98% patients with lupus nephritis, high titers with higher specificities, does not correlate with disease activity), anti-DS DNA antibody (may correlate with disease activity), complements (decreased C3 & C4 levels, correlate with disease activity).

• Treatment and prognosis: extreme variability in course of disease, treat active lupus nephritis with high dose steroids (1 mg/kg/day), if this fails or patient develops unacceptable side effects use immunosuppressive (azathioprine, cyclophosphamide), 5 year survival 90%.

• **Membranoproliferative GN:** idiopathic or secondary form due to SLE, RA, Sjogrens, leukemias/lymphomas, melanoma, endocarditis, hepatitis c/b, sarcoid

• Epidemiology: rare disease, type I more common than type II, whites>blacks.

• Clinical presentation: usually nephrotic syndrome (60%), acute nephritis syndrome (20%).

• Diagnosis: complement levels (decreased C3 and C4 in 60% cases, in type II).

• Pathology: type I-massive mesangial cellular and matrix proliferation, diffuse thickening of capillary wall (tram tracking due to double contour). IF reveals diffuse granular IgG, IgM and C3 deposits in mesangium and GBM; EM reveals subendothelial deposits. Type II-thickened GBM due to dense, irregular eosinophilic deposits, highly PAS positive, IF reveals intense C3 staining along capillary wall and bowmans capsule, EF with dense deposits in subepithelium. Type III-combination of above types.

• Prognosis and treatment: spontaneous remissions (10%), proteinuria (40%), CRI (10%), ESRD (45%). Treat with Ace and diuretic, possibly aspirin for mild disease; consider steroids for progressive disease.

*Immune complex-normal complement*

• **Visceral abscess nephritis:** chronic infections (osteo, dental/ intrathoracic/intra-abdominal abscesses).

• Clinical presentation: within weeks to years post initial infection, acute nephritic presentation, may see manifestations of cyroglobulinemia.

• Diagnostic tests: complements are normal, cryos are usually positive.

• Treatment and prognosis: depends on treatment of underlying infection.

• **IgA nephropathy/ Henoch-schonlein purpura:** idiopathic and secondary forms due to ETOH, IBD, sprue, psoriasis, AS, HIV

• Epidemiology: most common world wide GN, HSP children>adults, IgA 20-30 yo.

• Clinical presentation: usually asymptomatic microscopic hematuria or macroscopic hematuria with loin pain; rarely with acute nephritic syndrome (<2% cases).

• Diagnosis: normal serologies.
• Pathology: segmental mesangial proliferation, IF reveals IgA and C3 mesangial deposits; EM reveals mesangial deposits.
• Prognosis and treatment: supportive treatment, no effective interventions, and very good prognosis with spontaneous resolution in 15 %, CRI 60%, ESRD over 20 years 30%.

Pauci-immune (30%): small vessel vasculitis with minimal immune complex deposition; renal limited disease seen with idiopathic crescentic GN or associated with systemic syndromes of Wegeners granulomatosis, Micro-polyarteritis nodosum, Churg Strauss
• Epidemiology: uncommon, middle age, Caucasian > African American, men=women
• Clinical presentation: acute nephritic syndrome with RPGN, associated with pulmonary involvement (asthma, infiltrates, hemorrhage, nodules), upper respiratory tract (chronic sinusitis, ulcers), palpable purpura, GI complaints, neurologic involvement (neuropathy, headache)
• Pathology: segmental fibrinoid necrosis of vessel wall with neutrophil and lymphocyte infiltration , lumenal thrombosis and crescent formation.
• Diagnosis: PR3-ANCA (C-ANCA) positive in WG (75%), MPAN (40%), CS(10%); MPO-ANCA (P-ANCA) positive in renal limited GN (70%), MPAN (50%), WG(20%), CS (60%); normal compliments levels.
• Treatment and prognosis: NEED treatment to halt RPGN; high dose steroids, cyclophosphamide, azathioprine, plasmapheresis, renal transplant with ESRD.

Anti GBM disease (10%): renal limited Anti-GBM or systemic Goodpasture’s syndrome
• Epidemiology: young male predilection
• Clinical presentation: acute nephritic syndrome that progresses into RPGN, associated with pulmonary hemorrhage
• Diagnosis: Anti-GBM antibody
• Pathology: IF reveals linear ribbon-like deposition of IgG and C3 along basement membrane.
• Prognosis and treatment: very poor, nearly 80% progress to ESRD without treatment, treat emergently with plasmapheresis, steroids, cyclophosphamide.

Reasonable work up for patients with acute nephritic syndrome
1. Perform thorough history and physical, monitor UOP, confirm UA evidence of nephritis
2. Send serologies based on clinical suspicion: ANA, ASO, compliments, cryos, hepatitis B/C, ANCA’s, anti-gbm antibody, blood cultures
3. Follow clinical progression, look for signs of RPGN, if present, get immediate biopsy to provide timely intervention before progression to irreversible renal disease.
4. Watch out for the mimickers: malignant hypertension, TTP/HUS, atheroembolic disease, PAN, scleroderma

WHAT ABOUT RPGN? Must intervene early
• Definition: sudden deterioration of renal function within weeks associated with pathologic diffuse crescentic formation around glomeruli
• Pathogenesis: Complication of acute nephritic syndrome, can be seen with any of the above etiologies, usually due to overwhelming cell mediated immunity that incites powerful inflammatory response with subsequent macrophage and epithelial cell proliferation with fibrin deposition and crescent formation.

References: Schrier et al. Textbook of renal diseases., Up to Date