GLOMERULONEPHRITIS

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Approach to Glomerular Diseases: Clinical Presentation

Nephrotic Syndrome
- Heavy Proteinuria
- Low serum Albumin
- Edema
- High serum lipids

Nephritis
- Renal failure
- Hypertension
- Hematuria
  - Acute
  - Chronic
  - Rapidly Progressive

Asymptomatic Urinary Abnormalities

Urine Analysis
- Urinary RBC’s, sometimes deformed
- RBC Casts

- Large amounts Albuminuria
  ( >3g/Day )
Approach to Glomerulonephritis

1. Morphologic
2. Immunologic
3. Etiologic
4. Clinical

Vulnerability of Glomerulus to IC Injury

1. 20-25% of cardiac output
2. High glomerular capillary pressure
3. Fenestrated endothelium
4. Concentration (sieving effect)

Mechanisms of Immunologic Injury to the Glomerulus

1. Glomerular deposition of circulating Ag-Ab complexes
2. Binding of Circulating Ab to fixed glomerular Ag (i.e. anti-GBM Ab)
3. In situ immune complex formation

Glomerular Proliferation

1. Endocapillary

2. Extracapillary (crescentic)
Patterns of Glomerular Disease: Proliferation or Sclerosis

Approach to Glomerular Disease: Etiology
- History
- Physical Exam
- Laboratory, Radiological tests
- Primary Glomerular Disease
  - e.g. minimal change disease
- Secondary (Systemic) Disease
  - e.g. Lupus

- 7 year old child
- Several days of sore throat + low grade fever; he is given acetaminophen, and recovers uneventfully.
- 2 wks later develops dark, coca-cola colored urine and notes urinating less.
- Exam: pedal edema and elevated blood pressure.
- Labs:
  - Urine: rbc’s, rbc casts, 2+ prot.
  - Creatinine 2.4 mg/dl

Acute Nephritic Syndrome
- Decreased GFR
- Oliguria
- Edema
- Hypertension
- Active urine sediment
Etiology: Post-streptococcal GN

- Following infection with certain “nephritogenic” streptococcal strains (pharyngitic, dermal, etc)
- Children more common than adults
- Time lag from infection to onset of GN
- Nephritic picture common
- Low complement and C3
- Positive serologic tests for recent strep infection
- Prognosis: excellent in children; good in adults

Serum Complement Levels in Glomerulonephritis

- **Low Levels**
  - acute post-infectious GN
  - lupus nephritis
  - idiopathic MPGN
  - cryoglobulinemic GN
- **Normal Levels**
  - IgA nephropathy
  - ANCA-RPGN / Wegener’s / Microscopic PAN
  - Anti-GBM disease
  - Minimal change, FSGS, Membranous, Diabetes,
  - Amyloid, etc….

- A 16 year old high school junior notices dark brown urine after playing basketball.
- Labs:
  - Creatinine 1.1 mg/dl
  - Urinary sediment has rbc's and rbc casts.
  - Creatinine clearance 128 cc/min
  - 660 mg proteinuria/day
  - Serologic tests are normal or negative
Demographics of IgA Nephropathy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
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<tbody>
<tr>
<td>Ages</td>
<td>4 – 80 (mean 25) years</td>
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<td>(65% of patients in 2nd/3rd decade)</td>
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<td>M/F</td>
<td>2/1</td>
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<td>Rare in blacks</td>
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<td>Incidence (% primary glomerulopathies)</td>
<td>5-10% N. America</td>
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<td>Scandinavia</td>
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<td>20-30% Europe</td>
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<td>Australia</td>
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<td>25-45% Asia</td>
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Pathogenesis

1. Defective hepatic clearance
   - Liver cirrhosis
2. Increased IgA production
   - Association with elevated serum IgA
   - Onset may follow URI or Gastroenteritis
3. Defect of antigen exclusion at the mucosal surface
   - URI
   - Gastroenteritis
   - Celiac disease

Structure of Human Secretory IgA (sigA)
Henoch-Schönlein Purpura
Vasculitis with IgA-dominant immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles. Typically involves skin, gut & glomeruli, and is associated with arthralgias or arthritis.

Henoch-Schönlein Purpura
Schönlein-Henoch Purpura

- A 29 year old saleswoman develops arthritis of multiple joints, fever
- Exam: Lymphadenopathy, and a malar rash.
- Labs:
  - Urinalysis 3+ protein, 18-20 rbc’s
  - Creatinine 1.2 mg/dl
  - 24 hr. protein 1.8
  - Complement 18% (normal 50-150%)
  - ANA positive, Anti-DNA antibody positive

Etiology: IgA Nephropathy

- Most common idiopathic GN worldwide
- Defined by IgA deposition in mesangium
- Clinical Presentation
  - Young – gross hematuria
  - Adults – Proteinuria + hematuria
- Not “benign” hematuria (Berger’s Disease)
  - 20-30 % progress ESRD over 20 years
- Treatment Options
  - ACE inhibitor/AR blockers
  - Steroids
  - Fish Oil
  - Mycophenolate
Lupus Nephritis WHO Classification

Class II: Mesangial electron dense deposits

Class III: Focal segmental lupus nephritis

Class V: Membranous lupus nephritis with spikes
Treatment Approach to SLE Nephritis

Class I: Minimal mesangial LN (normal LM, + deposits)
- TREAT EXTRARENAL LUPUS

Class II: Mesangial proliferative LN
- TREAT EXTRARENAL LUPUS

Class III: Focal LN
- STEROIDS, CYTOTOXICS
  (<50% of all glomeruli)

Class IV: Diffuse LN
- STEROIDS, CYTOTOXICS
  (>50% of all glomeruli)

Class V: Membranous LN
- STEROIDS, CYTOTOXICS (in high risk pts)

Class VI: Advanced sclerotic LN (90% sclerosed, no activity)
- PREPARE FOR RENAL REPLACEMENT

Corticosteroids: Side Effects

Probability of Developing End-Stage Renal Disease with Different Treatment Regimens

Cyclophosphamide: Side effects

Strategies for Alternate Therapies

- Sequential cytotoxic therapy
  - Cyclophosphamide followed by Mycophenolate/Imuran
  - Mycophenolate
• A 58 year old insurance salesman develops sinusitis, weight loss, malaise and a dry cough over three weeks.
• His sinus films show opacification of the left maxillary sinus, and he is found to have a cavitary lesion on his chest X-ray.
• Labs:
  – Urinalysis: rbc's, wbc's, and rbc casts
  – Creatinine 2.7 mg/dl
  – Serum complement is normal
  – Anti-GBM antibodies are absent
  – ANCA is positive
Pulmonary-Renal Vasculitic Syndrome

- Pauci-immune (usually ANCA associated)
  - Wegener’s granulomatosis
  - Microscopic Polyangiitis
- Immune Complex Deposits (granular)
  - SLE
  - Cryoglobulinemic vasculitis
- Anti-Glomerular Basement Membrane Antibody Deposits (linear)
  - Goodpasture’s Syndrome

ANTIBODY MEDIATED GLOMERULONEPHRITIS

Circulating anti-GBM antibodies with linear complex localization with paucity of glomerular IF staining
Circulating ANCA with granular IF staining
Glomerular immune complex localization with granular IF staining

>80% ANCA+
Rapidly Progressive Glomerulonephritis

- Rapidly progressive renal failure (weeks)
- RPGN = Crescentic GN
- Pathogenesis
  - Anti-GBM disease
  - Immune complex GN
  - Pauci-immune GN
- Treatment and Course depend on etiology and stage

Treatment of Rapidly Progressive Glomerulonephritis

- Anti GBM Disease - Steroids, Cytotoxics, PTE
- Immune Complex GN - Treat Underlying Disease
- Pauci-immune RPGN - Cytotoxics (P.O. or I.V.)

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

- Anti proteinase-3 (PR3)
- Anti myeloperoxidase (MPO)

ANCA is to RPGN as Anti-DNA is to SLE