Glomerular Diseases in Primary Care

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Objectives

Discuss diagnosis of glomerular diseases
Identify Nephritic and Nephrotic syndromes
Review clinical features, diagnosis and treatment of glomerular emergency or RPGN

Glomerulonephritis
Asymptomatic Microscopic Hematuria

Nephritic Syndrome
  - Acute glomerulonephritis
  - Rapidly progressive glomerulonephritis
  - Chronic glomerulonephritis

Nephrotic Syndrome

Microscopic Hematuria

More than 2 RBC per HPF on a spun (3000 r.p.m for 5 minutes) urine sediment or some prefers number of RBC more than 10,000/ml of hemocytometer chamber.

Microscopic Hematuria

Glomerular origin (Dysmorphic): There is proteinuria, serum creatinine may be elevated with dysmorphic RBC & Renal referral/work up for GN

Non Glomerular origin (Isomorphic): Urology referral/Check upper U.tract by CT for stone, neoplasm, cystic disease etc. Consider need for cystoscopy.

Nephritic Syndrome

- Collection of findings associated with glomerular inflammation in proximity to endothelial surface
- Defined by hematuria, presence of dysmorphic RBCs or RBC casts on microscopic examination
- One or more of the following
  - Mild to moderate proteinuria
  - Mild to moderate edema
  - Hypertension
  - Increased creatinine
  - Oliguria
Clinical differences: Nephrotic vs Nephritic

<table>
<thead>
<tr>
<th></th>
<th>Nephrotic syndrome</th>
<th>Nephritic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>Gross &gt;3.5GM</td>
<td>Moderate &lt; 3GM</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>Reduced</td>
<td>Normal or mild reduction</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Absent or trace</td>
<td>Marked</td>
</tr>
<tr>
<td>Lipids</td>
<td>Marked elevation</td>
<td>Minimal elevation/normal</td>
</tr>
<tr>
<td>Edema</td>
<td>Marked</td>
<td>Moderate</td>
</tr>
<tr>
<td>Urine volume</td>
<td>Normal/reduced</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

Nephrotic Syndrome

- Minimal change disease
- FSGS
- Membranous Nephropathy
- Diabetic Nephropathy
- Amyloidosis
- Class V Lupus Nephritis

Nephritic syndrome

- Post infectious GN
- Lupus Nephritis class II, III, IV
- RPGN
  - Anti-GBM
  - Immune complex crescentic GN
  - Pauci immune, ANCA + crescentic necrotizing GN
- IgA nephritis & HSP
- MPGN I, II, III
Clinical Clues to Glomerular Diseases

Hematuria, Foamy urine, Elevation of Cr
• Pulmonary infection / infiltrate / Hemoptysis
• Hepatitis B, C & HIV infections
• Arthralgia
• Skin Rash
• Volume over load / new onset edema
• New onset Hypertension
• Diseases – Endocarditis, Shunt infection, SLE, Lymphoproliferative disorders etc
• IVDU

Tests for Glomerular Diseases

• CBC with diff, Renal panel, UA & Urine Protein and Creatinine Ratio
• C3, C4, Ch50
• ASO titre
• ANA, Anti Double Stranded DNA
• ANCA (C-ANCA, P-ANCA)
• Anti GBM Antibodies
• Serum Protein Electrophoresis, Serum Protein IF, Free light chain assay
• Hep-B, C and HIV

RPGN
Clinical condition that evolve with rapidly progressive decline in renal function and characterized by an inflammatory process that results in the formation of cellular crescents & called crescentic glomerulonephritis.

This is glomerular emergency.

Clinical presentation of RPGN

• Rapid loss of renal function
• Active urinary sediment
• Oliguria
• Hematuria/Proteinuria

How Crescents are formed?

Glomerular crescent formation is an etiologically nonspecific response to glomerular capillary rupture due to acute inflammatory injury

• Rupture of GBM → spillage of inflam. mediators
• Neutrophil margination
• Karyorrhexis
• Thrombosis
• Fibrin exudation
• Epithelial response

RPGN
Electron microscopy of RPGN

RPGN:Case

65 YO W male presents to the ER with 3 weeks history of arthralgia and fatigue & URI. On exam. BP is 150/80 and there is a petechial rash visible in lower extremities and also 1+ edema.
Hb is 9.4gm/dl, Creatinine 5.8mg/dl Urinalysis shows 20-50 RBC/hpf & 1+ protein.
CXR showed bilateral infiltrate.

RPGN:Case

What is the most likely cause of his renal failure?

A. Anti GBM disease
B. Lupus nephritis
C. Henoch Schoenlein purpura with crescentic GN
D. Cryoglobulinemia
E. ANCA associated vasculitis

3 major Immunopathologic categories of crescentic GN

- Type I
  - Anti-GBM crescentic GN
- Type II
  - Immune complex crescentic GN
    - Post infectious, SLE, IgA, MPGN, Fibrillary
- Type III
  - Pauci-immune crescentic GN
  - 80% ANCA positive

Crescentic GN and Systemic Vasculitis

75% of patients with ANCA GN have some sort of systemic small vessel vasculitis. GPA,MPA or EGPA

50-60% patients with Anti GBM disease have pulmonary capillaritis

Immune complex crescentic GN has the lowest frequency of systemic vasculitis. HSP, Cryoglobulinemic GN etc.

ANCA test methodology

- Immunofluorescence technique
  - On ethanol fixed neutrophils PR3-ANCA causes a characteristic cytoplasmic granular centrally accentuated immunofluorescence pattern called cANCA while MPO-ANCA causes a perinuclear pattern called pANCA
- Antigen specific testing
  - Antigen type (PR3 or MPO) is determined through antigen-specific methods. More specific
    - ELISA or capture ELISA
    - Bead based multiplex assay
- Appropriate paring is important for definitive DX
  - cANCA with PR3-ANCA & pANCA with MPO-ANCA
**Treatment of ANCA Vasculitis**

- Pulse steroids 1 GM daily for 3 days followed by Prednisone 1 mg / Kg daily
- Cyclophosphamide or Rituximab
- Plasmapheresis
  - Diffuse Alveolar hemorrhage
  - Severe Renal failure

**Types of Crescentic GN in consecutive Renal Biopsies in Univ. of North Carolina**

<table>
<thead>
<tr>
<th>Age</th>
<th>Pauci-immune crescentic GN</th>
<th>Immune complex crescentic GN</th>
<th>Anti-GBM crescentic GN</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>60% (77/632)</td>
<td>24% (154/632)</td>
<td>15% (92/632)</td>
<td>1% (9/632)</td>
</tr>
<tr>
<td>Age 1-20 (N=73)</td>
<td>42% (31/73)</td>
<td>45% (33/73)</td>
<td>12% (9/73)</td>
<td>0%</td>
</tr>
<tr>
<td>Age 21-60 (N=303)</td>
<td>48% (145/303)</td>
<td>35% (106/303)</td>
<td>15% (44/303)</td>
<td>3% (9/303)</td>
</tr>
<tr>
<td>Age &gt;60 (N=256)</td>
<td>75% (203/256)</td>
<td>6% (15/256)</td>
<td>15% (38/256)</td>
<td>0% (1/2560)</td>
</tr>
</tbody>
</table>

**RPGN Type I: Goodpasture’s Syndrome**

- Anti-GBM antibody-induced disease.
- Cells accumulate in Bowman’s space, form crescents.
- The Goodpasture antigen is a peptide within the noncollagenous portion of the α3 chain of collagen type IV.
- What triggers the formation of these antibodies is unclear
- There is linear deposition of antibodies and complement components along the GBM.

**RPGN Type I: Goodpasture’s Syndrome**

The anti-GBM antibodies cross-react with pulmonary alveolar basement membranes to produce the clinical picture of pulmonary hemorrhage associated with renal failure.
Treatment of Good Pastures Syndrome

- Plasmapheresis daily ASAP
- Pulse Steroids 1 GM daily for 3 days and then 1 mg / Kg daily
- Cyclophosphamide IV or PO

Frequency of crescents in different types of glomerular diseases in University of North Carolina.


<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Numbers</th>
<th>% with any crescents</th>
<th>% with &gt;50% crescents</th>
<th>Average % of crescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-GBM</td>
<td>126</td>
<td>97.3</td>
<td>84.8</td>
<td>77</td>
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<tr>
<td>ANCA GN</td>
<td>181</td>
<td>89.5</td>
<td>50.3</td>
<td>49</td>
</tr>
<tr>
<td>Lupus-Ii B IV</td>
<td>784</td>
<td>56.5</td>
<td>12.9</td>
<td>31</td>
</tr>
<tr>
<td>HSP</td>
<td>31</td>
<td>61.3</td>
<td>9.7</td>
<td>27</td>
</tr>
<tr>
<td>IgA</td>
<td>853</td>
<td>32.5</td>
<td>8</td>
<td>21</td>
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<tr>
<td>Post-infectious</td>
<td>120</td>
<td>53.3</td>
<td>3.3</td>
<td>19</td>
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<tr>
<td>Type I MPGN</td>
<td>107</td>
<td>33.8</td>
<td>4.6</td>
<td>25</td>
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<td>Type II MPGN</td>
<td>16</td>
<td>43.8</td>
<td>18.8</td>
<td>48</td>
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<tr>
<td>Fibrillary GN</td>
<td>101</td>
<td>22.8</td>
<td>5</td>
<td>26</td>
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<td>Mon. Ig dep. dx</td>
<td>54</td>
<td>5.6</td>
<td>0</td>
<td>13</td>
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<tr>
<td>TMA</td>
<td>251</td>
<td>5.6</td>
<td>0.9</td>
<td>20</td>
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<tr>
<td>Membranous</td>
<td>1092</td>
<td>3.2</td>
<td>0.1</td>
<td>15</td>
</tr>
</tbody>
</table>

RPGN
Which type of glomerulonephritis usually do not present as RPGN?

- A. IgA nephritis
- B. Lupus nephritis
- C. Fibrillary GN
- D. FSGS

IgA nephropathy

Autoimmune systemic disease – kidneys are bystanders

Defective glycosylation of IgA1 fraction with galactose deficiency

75% of patients with IgA nephropathy has galactose deficient IgA1 level above 90th percentile

Glomerular and tubular injury by immune complexes containing pathogenic IgA1

IgA Nephropathy

- In USA IgA nephropathy is the commonest glomerular disease
- In adults 1 case per 100,000
- In children 0.5 case per 100,000
- 10 times more common in Japan

Clinical outcome of IgA nephropathy

- Variable clinical course
- 96% 20 years renal survival if risk factors are absent
- Risk factors for dialysis or death are
  - Urine protein > 1GM
  - Hypertension BP > 140/90
  - Severity of the histologic lesion
  - Reduced renal function at the time of diagnosis

Treatment of IgA Nephropathy


Recommendation:
- ACEI/ARB if urine protein 0.5 to 1gm/day
- 6 month of steroids if urine protein > 1 gm after 3-6m of ACEI/ARB and GFR > 50
- Fish oil

BP Target:
- <130/80 if urine protein <1 g/day but <125/75 if >1 g/day

Rx of IgA with rapidly declining GFR

- Steroid + Cyclophosphamide for crescentic IgA (>50% glomeruli with crescents) with rapid deterioration in GFR
- Supportive care if kidney biopsy shows acute tubular injury and intratubular erythrocyte casts

Rx of IgA without proven benefit


- Steroids + Cyclophosphamide or Azathioprine, unless crescentic IgA with rapid decline in GFR
- Immunosuppressive Rx with GFR of <30 unless crescentic IgA nephropathy with rapid decline in GFR
- MMF
- Antiplatelet agents
- Tonsillectomy

Case: In Hospital

49 YO W obese male with DM & HTN is admitted with fever, chronic diabetic foot ulcer complicated by MRSA osteomyelitis. He became hypotensive and dehydrated but now improved with IVFs. He is on vancomycin. He received IV contrast 10 days ago for a CT scan.

Exam is unremarkable except bandaged Rt foot and bilateral lower extremities edema.

Labs: Creatinine 2.8 (was 1.3 6 days ago), Serum albumin 2.9, C3 is low but C4 normal. UA: ++ protein on dip and 23 RBC / HPF
Case: In Hospital
What is the cause of Renal Failure?

A. AKI - ATN from infection/sepsis & hypotension
B. Vancomycin Nephrotoxicity.
C. Contrast Induced Nephropathy
D. Glomerulonephritis

Infection related Glomerulonephritis

• APIGN
  – APSGN( Acute Post Strep GN)
  – Staph, GNR, Treponema, Salmonella, Brucella, Mycoplasma, Legionella, Borrelia, Bartonella, Coxeella
• Current Active Infection
  – Endocarditis, Shunt infection, Hepatitis C

Acute Diffuse Proliferative Glomerulonephritis

• Acute post-strep GN is the most common cause of this reaction pattern.
• Produces nephritic syndrome 2 weeks after a resp. or skin infection with "nephritogenic strain" of group A, beta-hemolytic streptococci.
• There is deposition of circulating immune complexes which fix complement and attract PMN's.

Acute Diffuse Proliferative Glomerulonephritis

• There is swelling & proliferation endothelial cells
• This chokes off their blood supply, making the gloms hypercellular and bloodless
• This explains the oliguria, edema, and hypertension
• Deposits of circulating immune complexes fix complement and attract neutrophils

Acute Diffuse Proliferative GN: Post-strep. GN Outcome

• Children: 95% recover
• Adults:
  – Usually good prognosis.
  – Some develops rapidly progressive disease, chronic renal failure may cause ESRD
Systemic Lupus Erythematosus

• The kidney is a frequent target of injury in SLE.
• Mechanism of injury is immune complex deposition in mesangium, endothelium & glomerular basement membranes
• Other forms of injury may include a thrombotic process involving the glomerular capillaries & extraglomerular vasculature, thought to be caused by antiphospholipid antibodies.

WHO Classification of Lupus Nephritis

Class I
Minimal or no detectable abnormalities, rare, seen in renal biopsies from less than 5% of SLE patients.
Class II
Mesangial lupus glomerulonephritis
Class III
Focal proliferative glomerulonephritis
Class IV
Diffuse proliferative glomerulonephritis
Class V
Membranous glomerulonephritis

None of these patterns are specific for lupus

Systemic Lupus Erythematosus

• Antinuclear antibody, an antibody to nucleosomal DNA-histone complexes, is very sensitive but not specific.
• Anti-ds (double stranded) DNA is more specific for lupus. This test may correlate with the degree of activity of lupus, in general, and with the level of nephritis.
• Antiphospholipid antibody is present in 30% of patients with SLE. This is associated with thromboembolic complications.

Pulmonary- Renal Syndrome

• Goodpasture’s disease
• Granulomatous polyangiitis
• Microscopic polyangiitis
• SLE
• Cryoglobulinemia
• ARF with pulmonary edema/embolism/pna

Thank You For Your Attention