INTERNAL MEDICINE CORE CURRICULUM

NEPHRITIS SYNDROMES

Wei Ling Lau, MD
Assistant Professor, Nephrology
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COMMON SCENARIO IN RENAL CLINIC

- 32 year old Asian female seen as new consult
- Microscopic hematuria
- Low-grade proteinuria 400 mg/day
- Normotensive without meds, BP 108/65, no DM
- Normal Cr 0.6
- Urine sediment shows 3-5 normomorphc RBCs per HPF
Angiotensin II vasoconstricts
IgA nephropathy

- Abnormal glycosylation of IgA1 → mesangial deposits
- Recurrent episodes of gross hematuria typically <5 days following a bacterial or viral URI
  - Longer latent period from time of URI to onset of hematuria for post-infectious GN; 1-3 weeks with group A beta-hemolytic Strep pharyngitis; 3-6 weeks after streptococcal skin infection
- 20-40% of patients will progress to end-stage kidney failure within 20 years of presentation
Immunofluorescence microscopy showing mesangial immunoglobulin A (IgA) deposits
Therapy of IgA nephropathy

- RAAS blockade with target BP <130/80 and proteinuria <500 mg/day
- Prednisone for 4-6 months in patients who have nephrotic syndrome (5% of cases) and minimal fibrosis on kidney biopsy.
- Prednisone also helpful to prevent deterioration in renal function in patients with moderate proteinuria 1.5-3.5 g/day.
- Conflicting reports about efficacy of fish oil (omega-3 fatty acids) at a dose of 12 g/day. Deficiencies of essential fatty acids have been detected in IgA nephropathy, and fish oil is rich in long-chain omega-3 polyunsaturated fatty acids. These produce altered and less biologically effective prostaglandins and leukotrienes, as well as reduced platelet aggregation.
LET’S CHANGE SOME PARAMETERS...

- 67 year old female
- c/o occasional left flank pain
- Microscopic hematuria
- Tobacco use history 35 pk years
- BP 140/70 on lisinopril 5 mg daily
- Stable Cr 1.4 with eGFR 54
- Low-grade proteinuria 480 mg/day (CKD stage G3aA3)
- Urine sediment shows 3-5 normomorph RBCs per HPF, 3-5 WBCs per HPF
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DDx:
- Infection
- Kidney stones
- Bladder CA
IgA vasculitis spectrum: Henoch-schonlein purpura

- Small-vessel vasculitis
- Most common in kids; 90% of cases in kids <10 yrs old, usually after a URI
- Kidneys affected (40% of cases) PLUS skin, joints, gut
- Classic triad:
  - Purpura (100%)
  - Arthritis / joint pains (80%)
  - Abdominal pain (62%)
- GI bleeding in 33% of cases, sometimes due to intussusception
- Supportive therapy, good prognosis (90% of cases have full recovery)
RAPID LOSS OF GFR

- 67 y/o female PMHx HTN, obesity, CHF
- Presents with fatigue, fever, anorexia, diarrhea 1 week prior, bilat wrist and finger joint arthritis, BLE edema
- Cr 3.4 from baseline 1.1 measured at PCP’s office 2 months ago
- Spot urine protein:Cr ratio 1.8 g/g
- Urine sediment with muddy brown casts
- CXR clear, blood and urine cx negative
RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

- Rapid decline in eGFR of $>50\%$ within 3 months
- Marked reduction in eGFR limits rate of protein filtration
- Pathologic finding: extensive glomerular crescent formation at sites of focal rupture of the glomerular capillary tufts.
- Active necrotizing lesions with fibrin exudate
- Advanced disease: fibrocellular and fibrous crescents, collagen deposition
Dysmorphic RBCs

Crenated RBCs
<table>
<thead>
<tr>
<th>Type I RPGN (Anti-GBM Antibody) (linear pattern by IF)</th>
<th>3% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal limited (antibody against noncollagenous portion $\alpha_3$ chain of collagen type IV)</td>
<td></td>
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<tr>
<td>Goodpasture syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Type II RPGN (Immune Complex) (granular pattern by IF)</strong></td>
<td>45%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
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<tr>
<td>Postinfectious glomerulonephritis</td>
<td></td>
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<tr>
<td>Systemic lupus erythematosus (lupus nephritis)</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy and Henoch-Schönlein purpura</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Type III RPGN (Pauci-Immune) (no staining by IF)</strong></td>
<td>50%</td>
</tr>
<tr>
<td>ANCA (anti-neutrophil cytoplasmic antibody)-associated vasculitis</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>“Wegener granulomatosis” (granulomatosis with polyangiitis)</td>
<td></td>
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<tr>
<td>Microscopic polyangiitis</td>
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</tbody>
</table>
LOW C3 GLOMERULOPATHIES (ALTERNATIVE COMPLEMENT PATHWAY ACTIVATION)

Immune complex glomerulonephritis syndromes

- Any crescentic GN or RPGN
- Membranoproliferative GN
- Post-infectious GN – check antistreptolysin (ASO), anti-DNAse B
- Lupus nephritis – check ANA, anti-dsDNA
- Cryoglobulinemia – check cryoglobulin titers, screen for Hep B/C
- Bacterial endocarditis – check Echo, blood cultures
<table>
<thead>
<tr>
<th></th>
<th>Ethanol-fixed neutrophils</th>
<th>Formalin-fixed neutrophils</th>
<th>MPO ELISA</th>
<th>PR3 ELISA</th>
<th>Disease Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C-ANCA</strong></td>
<td>Granular Cytoplasmic</td>
<td>Granular Cytoplasmic</td>
<td>Neg</td>
<td>Pos</td>
<td>Wegener’s Granulomatosis; Churg-Strauss Syndrome</td>
</tr>
<tr>
<td><strong>P-ANCA</strong></td>
<td>Perinuclear</td>
<td>Granular Cytoplasmic</td>
<td>Pos</td>
<td>Neg</td>
<td>Microscopic Polyangiitis</td>
</tr>
<tr>
<td>Atypical C-ANCA</td>
<td>Fine, flat speckled</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>No known disease association</td>
</tr>
<tr>
<td>Atypical P-ANCA</td>
<td>Very rim</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Ulcerative Colitis; Primary Sclerosing Cholangitis</td>
</tr>
<tr>
<td><strong>ANA</strong></td>
<td>Nuclear; Lymphocyte nuclei</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Multiple non-vasculitic diseases</td>
</tr>
<tr>
<td></td>
<td>Clinical Signs</td>
<td>Serology</td>
<td>Biopsy</td>
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<tr>
<td>Immune-complex</td>
<td>Infection or lupus or IgAN history</td>
<td>↓ C3 (except IgAN) ANA+ if lupus</td>
<td>IgG &amp; C3 deposits (or IgA deposits in IgAN)</td>
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<tr>
<td>Anti-GBM</td>
<td>Pulmonary hemorrhage ‘Goodpastures’</td>
<td>Anti-GBM antibody</td>
<td>Linear IgG deposits</td>
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<tr>
<td>Pauci-immune</td>
<td>Skin rash, Pulm hemorrh, upper respiratory granuloma ‘Wegeners’ (GPA)</td>
<td>ANCA antibody</td>
<td>No immune deposits</td>
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PULMONARY-RENAL SYNDROME

Acute GN and pulmonary hemorrhage DDx:

1. ANCA-positive vasculitis: Granulomatosis with polyangiitis, microscopic polyangiitis
2. Anti-GBM antibody disease (Goodpasture’s)
3. Rare cases: lupus, Henoch-Schonlein purpura
4. Pulmonary pathology not directly related to GN: pulmonary edema due to fluid overload, pulm emboli, PNA, infective endocarditis
THERAPY OF RPGN

• Need early diagnosis and initiation of therapy to minimize degree of irreversible kidney injury
• Pulse methylprednisolone followed by daily oral prednisone
• Oral or IV cyclophosphamide, or rituximab
• +/- plasmapheresis
• If there is delay in obtaining kidney biopsy but there is high suspicion for RPGN, can begin empiric therapy with pulse methylprednisolone 500-1000 mg/day for 3 days +/- plasmapheresis especially if pt has hemoptysis and positive anti-GBM antibody
• Considerations: advanced fibrosis on kidney biopsy; recent cancer; frail geriatric patient; fertility in young patients.
POST-INFECTION CASE

• 43 y/o Hispanic male from Santa Ana, does not have PCP
• DM diagnosed 3 years ago, inconsistently taking metformin
• Stepped on a nail 4 weeks ago, went to an Urgent Care and has completed a course of Keflex
• Presents with mixed nephrotic/nephritic picture: bilat LE edema, proteinuria 4.5 grams/day, BP 155/90, UA with 3-5 RBCs per HPF and scattered granular debris.
• Normal serum Cr 0.8 mg/dL
• Low C3 and normal C4, serum albumin 3.3 g/dL
C3 humps on immunofluorescence
THERAPY FOR POST-INFECTIONOUS GN

- Supportive care
- Make sure infection is treated
- BP meds
- Diuretics to manage LE edema
- Steroids, immunosuppressive agents and plasmapheresis generally NOT indicated
SUMMARY: CHARACTERISTICS OF NEPHRITIC SYNDROME

- Hematuria with RBC casts, dysmorphic RBCs
- Hypertension
- Proteinuria 1-3 g/day
- +/- edema
- +/- acute kidney injury
- Rapidly progressive GN: AKI with rapid decline in eGFR of >50% within 3 months associated with systemic symptoms
  - Kidney biopsy, pulse high-dose steroids, cyclophosphamide or Rituxan, plasmapheresis if pulm hemorrhage
  - Usually no immunosuppression for post-infectious GN
QUIZ QUESTION #1

All of the following are features of nephritic syndrome EXCEPT:

a. Hypertension
b. Urine WBCs
c. Urine RBC casts
d. Proteinuria 1-3 grams/day
Immunosuppression with pulse methylprednisolone and cyclophosphamide is indicated in the following patients presenting with hematuria EXCEPT:

a. 45 year old male with serum Cr 2.8 (baseline Cr 1.0), proteinuria 2.5 grams/day, bilat LE edema, low complement C3, treated for Streptococcal cellulitis 4 weeks prior. Kidney biopsy shows characteristic sub-endothelial “humps” (C3 deposits).

b. 39 year old female with serum Cr 3.5 (baseline Cr 1.1), proteinuria 5 grams/day, malar rash, alopecia, arthritis of small joints, with positive ANA and elevated anti-dsDNA titer of 1:320. Kidney biopsy shows diffuse proliferative glomerulonephritis pattern with “full house” immunofluorescence (positive staining for C3, C4, IgG, IgA, IgM).

c. 68 year old female with serum Cr 5.0 (baseline Cr 1.0), proteinuria 1.8 grams/day, oliguria, bilat LE edema, positive c-ANCA, arthralgias and fatigue. Kidney biopsy shows necrotizing fibrinous crescents in 50% of glomeruli, with negative immunofluorescence staining.

d. 42 year old female with serum Cr 2.5 (baseline Cr 0.8), proteinuria 3 grams/day, BP 155/90, history of gross hematuria episodes 3-5 days following upper respiratory tract infections. Kidney biopsy shows mesangial deposits and exudative crescents in 50% of glomeruli.