Pulmonary Renal Syndromes

Henry Mroch, MD, FACP FASN
Providence Sacred Heart Medical Center, Spokane
WSU Elson S. Floyd College of Medicine

November 2020
Disclosures

• None
Objectives

• Review the pathophysiology of rapidly progressive glomerulonephritis

• Discuss the evaluation and treatment of immunologic, rapidly progressive kidney diseases

• Describe the natural history and clinical courses of anti-glomerular basement membrane disease and ANCA associated vasculitis

• Review avacopan as a potentially emerging treatment option for ANCA associated vasculitis
Cases

- 64 year old teacher. No PMH, no medications. Smokes 1/2 ppd cigarettes.
- He presented to urgent care with “sinus congestion” and a new onset headache and blurring vision. No cough, no hemoptysis.
- BP 250/155 —> ICU admission
- Creatinine 3.8 mg/dl
- ESR 102, anti-GBM ++, negative ANCA, ANA, ASO, anti-cardiolipin
- “Active” urine sediment
- Renal biopsy

- 71 year old retired presents with migratory arthralgia, dyspnea, fatigue and an urticarial rash. PMH hypertension on HCTZ
- BP 155/95
- Creatinine 1.0 —> 3.4 mg/dl
- CXR - RUL infiltrate
- ESR 94, pANCA (MPO) ++, negative anti-GBM, ANA, ASO, anti-cardiolipin
- “Active” urine sediment
- Renal biopsy
Which best describes the clinical picture of acute nephritic glomerulonephritis?

A. 6 grams proteinuria; bland sediment; normal creatinine
B. 1 gram proteinuria; granular casts; increased creatinine
C. 2 grams proteinuria; dysmorphic RBCs; increased creatinine
D. 3 grams proteinuria; bland sediment; increase creatinine
**Common Glomerular Disorders**

**Nephrotic**
- Proteinuria ~ 3 grams +;
- RBC negative

**Nephritic**
- Proteinuria ~ 1-3 grams;
- RBC positive

- **Podocyte disorders outside the vasculature**
- **Inflammation of vascular endothelium**

**Diabetes**

**Amyloid**

**Anti-GBM**
**ANCA vasculitis**
**SLE Class IV (DPGN)**
**IgA vasculitis**

**Podocyte disorders outside the vasculature**

**Inflammation of vascular endothelium**

Henry Mroch, MD. 2020
Hints of glomerular bleeding

RBC Cast

Dysmorphic RBCs
Which best describes the clinical picture of acute nephritic glomerulonephritis?

A. 6 grams proteinuria; bland sediment; normal creatinine

B. 1 gram proteinuria; granular casts; increased creatinine

C. 2 grams proteinuria; dysmorphic RBCs; increased creatinine

D. 3 grams proteinuria; bland sediment; increase creatinine
Crescentic RPGN by Mechanism

- Anti-GBM - 15%
- ANCA (AAV) - 60%
- Immune complex:
  - SLE(Class IV) - 25%
  - MPGN
  - Endocarditis
  - Post infectious
  - IgA vasculitis

Electron dense immune complexes
Anti-GBM Disease

- 1 per million people/year incidence
- Bimodal: 20-40 years and >60 years (more often renal only)
- Linear Ig staining of the basement membrane
- 15% of all RPGN
- Classic Goodpasture’s = Pulmonary hemorrhage + RPGN (90%)
- Presentation is commonly SEVERE injury
Exposure of sequestered epitopes within GBM (lungs + kidney) - **NC1 COL4(3)**

- Smoking
- Infection
- Solvents
- Other

Anti-GBM Ab formation
ANCA Associated Vasculitis

- 20-40 per million people/year incidence
- 60-80% of RPGN cases
- ~80% will have renal involvement
- Pauci-immune necrotizing vasculitis with crescents
- Immunofluorescence staining will be faint to absent
Aberrant expression of PR3 and MPO in n

Figure 1. Pathogenesis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA autoantigens (proteinase 3 [PR3] and myeloperoxidase [MPO]) are normally sequestered in the primary granules of neutrophils. Infection or other environmental stimuli result in neutrophil priming, with movement of PR3 and MPO to the cell surface. Binding of ANCA to these autoantigens results in activation of neutrophils, which adhere to vascular endothelium. Neutrophil degranulation leads to the release of reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), damaging the endothelium. Chemokines and tissue deposition of PR3 and MPO result in the recruitment of autoreactive T cells and monocytes augmenting tissue injury. Drawings created with BioRender.
Keep in mind the spectrum of clinical presentation of anti-GBM and ANCA vasculitis.
PR3 and MPO are the ANCA antigens

Table 1. Frequency of ANCA Positivity in Different Conditions

<table>
<thead>
<tr>
<th>Conditions</th>
<th>PR3-ANCA (mostly cANCA)</th>
<th>MPO-ANCA (mostly pANCA)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA-Associated Vasculitis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GPA</td>
<td>75%</td>
<td>20%</td>
<td>5% ANCA negative</td>
</tr>
<tr>
<td>MPA</td>
<td>30%</td>
<td>60%</td>
<td>10% ANCA negative</td>
</tr>
<tr>
<td>EGPA</td>
<td>5%</td>
<td>45%</td>
<td>50% ANCA negative</td>
</tr>
<tr>
<td>Renal-limited vasculitis</td>
<td>10%</td>
<td>80%</td>
<td>10% ANCA negative</td>
</tr>
<tr>
<td>Drug-induced vasculitis</td>
<td>10%</td>
<td>90%</td>
<td>Often high titer, dual positivity for MPO and PR3</td>
</tr>
<tr>
<td>Nonvasculitis Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>2%</td>
<td>10%</td>
<td>10% atypical ANCA</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>15%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Negative</td>
<td>Negative</td>
<td>Atypical ANCA, various antigens: ulcerative colitis (50%-67%), Crohn disease (6%-15%)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>Negative</td>
<td>Negative</td>
<td>Atypical ANCA, various antigens: 60%-80%</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Negative</td>
<td>Negative</td>
<td>Atypical ANCA pattern, directed against BPI (90%)</td>
</tr>
</tbody>
</table>

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BPI, bactericidal/permeability-induced protein; cANCA, cytoplasmic antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, proteinase 3.
Cyclophosphamide and Rituximab are com

Table 1 Randomized controlled trials for induction of remission in antineutrophil cytoplasmic antibody associated vasculitides with renal involvement and cyclophosphamide-sparing regimens

<table>
<thead>
<tr>
<th>Name of the Trial (number of patients)</th>
<th>Inclusion criteria</th>
<th>Treatment groups (drug dose)</th>
<th>Primary end points</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCOPS[7] (149)</td>
<td>New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150-500 μmol/L (1.7-5.66 mg/dL)</td>
<td>Intravenous pulse CYC (15 mg/kg) vs Daily oral CYC (2 mg/kg)</td>
<td>Remission, Time to relapse</td>
<td>Pulse CYC not inferior to oral CYC Less leucopenia and trend towards more relapses with pulse CYC</td>
</tr>
<tr>
<td>CORTAGE[8] (104)</td>
<td>New diagnosis of MPA, GPA, EGPA, PAN and age &gt; 65 yr</td>
<td>Rapid CCS tapering and reduced-dose intravenous pulse CYC (500 mg) vs Standard intravenous pulse CYC (500 mg/m²)</td>
<td>Severe adverse events</td>
<td>Less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates</td>
</tr>
<tr>
<td>RAVE[10] (197)</td>
<td>New or relapsing GPA or MPA, creatinine ≤ 353.6 μmol/L (4 mg/dL)</td>
<td>RTX (4 × 375 mg/m² infusions) vs Daily oral CYC</td>
<td>Complete remission and cessation of CCS at 6 mo</td>
<td>RTX not inferior to oral CYC, RTX better in patients with relapse than after first diagnosis</td>
</tr>
<tr>
<td>RITUXVAS[11] (44)</td>
<td>New diagnosis of AAV and severe renal involvement</td>
<td>RTX (4 × 375 mg/m² infusions) plus two intravenous pulses of CYC vs intravenous pulse CYC only</td>
<td>Sustained remission</td>
<td>RTX not inferior to pulse CYC</td>
</tr>
</tbody>
</table>

AAV: Antineutrophil cytoplasmic antibody associated vasculitides; CYC: Cyclophosphamide; RTX: Rituximab; CCS: Corticosteroids; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; PAN: Polyarteritis nodosa.

** IMPROVE Trial 2010 CYC induction —> MMF vs. AZA maintenance MMF less effective than AZA

World J Nephrology, May 2018
PEXIVAS Trial
A perPLEXing ANCA Treatment

Plasma Exchange and Glucocorticoids for ANCA-Associated Vasculitis

PEXIVAS, A MULTICENTER, RANDOMIZED, 2X2 FACTORIAL TRIAL

N=704 Patients

Death from any cause or end-stage kidney disease

Plasma Exchange

No Plasma Exchange

Standard-Dose Glucocorticoids

Reduced-Dose Glucocorticoids

![Diagram showing treatment outcomes](image)

- Plasma Exchange: 28.4% (100/352)
- No Plasma Exchange: 31.0% (109/352)
- Standard-Dose Glucocorticoids: 25.5% (83/325)
- Reduced-Dose Glucocorticoids: 27.9% (92/330)

P=0.27

Noninferiority margin, 11 percentage points

No significant differences in serious adverse events
Serious infections at 1 yr less common with reduced-dose glucocorticoids

M. Walsh et al. 10.1056/NEJMoa1803537

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Avacopan treatment for ANCA disease
C5a receptor antagonist

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis


JASN September 2017, 28 (9) 2756-2767; DOI: https://doi.org/10.1681/ASN.2016111179
Avacopan for Steroid Avoidance in ANCA-Associated Vasculitis

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis


### Step 1

- **IV Cyclophosphamide and Azathioprine**
  - 12 patients
  - Avacopan 30 bid
  - Placebo bid
  - Prednisone 60

### Step 2

- **IV Cyclophosphamide and Azathioprine**
  - 14 patients
  - Avacopan 30 bid
  - Placebo bid
  - Prednisone 60

### Step 3

- **Cyclophosphamide + Azathioprine OR Rituximab**
  - 41 patients
  - Avacopan 30 bid
  - Prednisone 20
  - Placebo
  - Prednisone 60

### Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement in BVAS Score</th>
</tr>
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<tbody>
<tr>
<td>Avacopan 30 bid</td>
<td>81%</td>
</tr>
<tr>
<td>Placebo bid + Prednisone 60</td>
<td>86%</td>
</tr>
<tr>
<td>Prednisone 60</td>
<td>70%</td>
</tr>
</tbody>
</table>

Both avacopan groups met noninferiority criteria.

### Adverse effects

Incidence of all adverse events and grade 3 or greater adverse events was similar across groups.
Dual-positive anti-GBM + ANCA antibodies

- ~30% of anti-GBM test positive for ANCA (almost MPO exclusively)

- Speculative mechanism: ANCA activity exposes sequestered GBM epitopes

- Severe disease at presentation, like anti-GBM with early morbidity and mortality

- Long term course involves relapses similar to ANCA associated vasculitis
### Epilogue

- **64 year old teacher.** No PMH, no medications. Quit smoking. Cr 3.8 mg/dl.

  - Renal biopsy showed 16/17 gloms with crescents and necrosis with **linear staining of GBM**
  - Tx: Cyclophosphamide, steroids, plasmapheresis
  - Cr 3.8 —> 7.5 mg/dl
  - ESRD with HD now on CCPD
  - Anti-GBM Ab is now negative
  - Nearing a living donor kidney transplant

- **71 year old retired** presents with migratory arthralgia, fatigue and an urticarial rash. Cr 3.4 mg/dl

  - Renal biopsy showed 66 gloms (80% necrotizing crescents) with **negative immunofluorescence Ab staining**
  - Tx: Rituximab + steroids (she tolerated steroids poorly due to anxiety)
  - Creatinine 3.4 —> 1.1 mg/dl
  - pANCA normalized, then relapsed in second year with Cr 3.1 mg/dl
  - Re-Tx: Rituximab + steroids
  - Cr 2.4 —> 1.2 mg/dl
Pulmonary-renal syndromes may present with vague or multiple system symptoms

Check urinalysis and renal biopsy urgently, if possible

Anti-GBM is typically a “single storm” syndrome not requiring long term maintenance immunosuppression and low transplant recurrence

ANCA vasculitis with renal involvement presents as RPGN with organ and potentially life-threatening symptoms

Medications can lead to ANCA antibody formation
Key Points

• First line therapy {cyclophosphamide vs rituximab} + steroids

• PR3 ANCA relapse more frequently than MPO ANCA

• Recurrence of ANCA with previously cleared ANCA antibody is associated 75% relapse

• Avacopan (C5a receptor antagonist) is an emerging non-steroid option with demonstrated non-inferiority to high dose steroids in ANCA patients
Additional References

Anti-Glomerular Basement Membrane Disease; CJASN July 2017, 12 (7) 1162-1172;
DOI: https://doi.org/10.2215/CJN.01380217

DOI: 10.1053/j.ajkd.2019.04.031
Thank you for all you do! Be well, be safe!