Case 3

Clinical history

- 57-year-old man, elevated serum creatinine, proteinuria, and hematuria
- Medical history:
  - Diabetes mellitus for 8 years, no retinopathy.

Laboratory results

- 3 grams/day proteinuria
- Microscopic hematuria
- Serum creatinine 3.5 mg/dl
- Serum albumin 2.9 g/dl
- Serum and urine protein electrophoresis and immunofixation negative
- ANA, ANCA, and anti-GBM studies were negative
Summary of biopsy findings

- LM: Mesangial and endocapillary hypercellularity, segmental GBM duplication
- IF: bright linear GBM staining for IgG lambda
- EM: Subendothelial lucency, GBM duplication; no deposits in GBM or TBM
Diagnosis

- “Atypical” anti-glomerular basement membrane (GBM) nephritis

Typical Anti-GBM disease

- Circulating antibodies against an antigen in the GBM
- Clinical:
  - Acute kidney injury, hematuria, proteinuria
  - Pulmonary hemorrhage in 34%-62%
  - Anti-GBM antibody production & disease is short-lived

- Rare: ~1 case per 2 million per year
- Treatment: plasmapheresis, steroids, cyclophosphamide
- Poor renal survival: untreated, >90% death or dialysis

Kidney biopsy: Typical anti-GBM disease

- LM: Diffuse necrotizing & crescentic GN
  - Active lesions are same “age”
  - Unaffected areas of glomeruli appear normal
- IF: Bright linear GBM staining for polyclonal IgG
- No immune complex deposits
Typical anti-GBM disease
Diffuse crescents

IgG  Linear GBM staining

IgG  Focal tubular basement membrane staining

**Anti-GBM antibodies**

- Autoantibodies against the non-collagenous domain 1 of the α3-chain of type IV collagen (α3(IV)NC1), “Goodpasture antigen”

- Disease requires conformational change in α3NC1 and α5NC1 subunits
  - Exposes cryptic epitopes
  - “Conformeropathy”
Structure and Composition of Type IV Collagen and the Chromosomal Location of the Genes Encoding Its Six Isoforms.


Antigen modification in anti-GBM disease

- Potential causes: smoking, infection, lithotripsy, inhaled hydrocarbons, cocaine use
- HLA DRB1*15:01-positive have an 8.5-fold greater relative risk
- Antigen modification versus loss of tolerance

“Atypical” anti-GBM nephritis

- Linear GBM staining for immunoglobulins by IF but without the typical light microscopy appearance of anti-GBM disease

Methods

Renal pathology records were searched for biopsies with linear GBM staining for immunoglobulins

Clinical features, laboratory tests, and biopsies were reviewed

Patients: Atypical anti-GBM disease

- 20 adults (9F, 11M)
- Mean age of 54 years (range 18-85)
- 70% had hypertension (new-onset or longstanding)
- 50% were current smokers and 15% were former smokers


Clinical presentation

- Increased creatinine
  - Median SCr at biopsy 1.9 mg/dl (range 0.9-4.6)
- Proteinuria (in all)
  - Nephrotic-range in 10 (50%)
  - 35% had full nephrotic syndrome
- Hematuria
  - 90% had microscopic hematuria
  - 20% had gross hematuria
- No pulmonary involvement

Laboratory results

- ANCA, ANA, hepatitis B negative in all tested patients
- Hepatitis C Ab positive in one patient (negative viral load)
- Serum C3: normal in 94%
- Serum C4: normal in 88%
Laboratory results

- ANCA, ANA, hepatitis B negative in all tested patients
- Hepatitis C Ab positive in one patient (negative viral load)
- Serum C3: normal in 94%
- Serum C4: normal in 88%
- Negative serum anti-GBM by ELISA/multiplex immunoassay in all patients

Renal biopsy: light microscopy

- Heterogeneous glomerular features, may overlap
- All show mesangial and/or endocapillary hypercellularity
  - Most common: endocapillary proliferative GN (50%)
  - MPGN (chronic TMA) pattern in ~20%
  - Focal segmental glomerulosclerosis in 2 (10%)
  - Nodular glomerulosclerosis (literature)
  - Two showed segmental burnt-out membranous GN

Renal biopsy: light microscopy

- Focal cellular or fibrocellular crescents in 40% of cases
- Features of glomerular microangiopathy (thrombotic microangiopathy, TMA) in 40% (electron microscopy)

Immunofluorescence

- Linear GBM staining for immunoglobulin heavy chain (usually IgG) and light chain(s)
- Focal linear TBM staining in 45%
- Polytropic IgG in 10 (50%) (IgG, κ, λ)
- Light chain restriction in 10 (50%)
  - IgG λ in 6
  - IgG κ in 1
  - IgM κ in 2
  - IgA λ in 1
Electron microscopy

- Features of glomerular microangiopathy in 8/20 (40%)
- Absence of electron-dense immune complex-type deposits
- Absence of finely granular "powdery" deposits in basement membranes

Comparison Between Polytypic and Monotypic Atypical Anti-GBM Nephritis

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=20)</th>
<th>Polytypic anti-GBM nephritis (n=10)</th>
<th>Monotypic Anti-GBM nephritis (n=10)</th>
<th>p*</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (55%)</td>
<td></td>
<td>4 (40%)</td>
<td>7 (70%)</td>
<td>0.37</td>
<td>NS</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>58 (18-85)</td>
<td>60 (18-85)</td>
<td>58 (19-77)</td>
<td>0.53</td>
<td>NS</td>
</tr>
<tr>
<td>Median serum creatinine in mg/dl (range)</td>
<td>1.9 (0.9-4.6)</td>
<td>2.4 (1.0-4.6)</td>
<td>1.7 (0.9-3.5)</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Median 24h urine protein in g/day</td>
<td>3 (0.3-25)</td>
<td>7.6 (0.7-25)</td>
<td>1 (0.3-15)</td>
<td>0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Median serum albumin in g/dl (range)</td>
<td>3.3 (2.1-4.6)</td>
<td>2.8 (2.1-4.1)</td>
<td>3.4 (2.1-4.1)</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>7 (35%)</td>
<td>5 (50%)</td>
<td>2 (20%)</td>
<td>0.35</td>
<td>NS</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/19 (93%)</td>
<td></td>
<td>10/10 (80%)</td>
<td>1/9 (10%)</td>
<td>1.00</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of follow up in months (range)</td>
<td>40 (3-41)</td>
<td>24 (3-52)</td>
<td>57 (8-61)</td>
<td>0.02</td>
<td>S</td>
</tr>
<tr>
<td>1-year rate of patient survival</td>
<td>13/14 (93%)</td>
<td>6/7 (86%)</td>
<td>7/7 (100%)</td>
<td>1.00</td>
<td>NS</td>
</tr>
<tr>
<td>1-year rate of renal survival (in surviving patients)</td>
<td>11/13 (85%)</td>
<td>4/6 (67%)</td>
<td>7/7 (100%)</td>
<td>0.19</td>
<td>NS</td>
</tr>
</tbody>
</table>

Clinical follow-up of atypical anti-GBM disease

- 1-year rates
  - 93% patient survival
  - 85% renal survival (in surviving patients)
- 25% progressed to ESRD (average f/u 28 months, range 1-61)
- 69% had persistent renal dysfunction with unremitting hematuria, proteinuria, and/or elevation of serum creatinine
### Treatment and Outcome Summary

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration of follow-up (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pred/Cyclophosphamide (CYT)</td>
<td>3</td>
<td>died (final SCr 1.6)</td>
</tr>
<tr>
<td>MP/Pred/CYT/PLX</td>
<td>27</td>
<td>ESRD 1 month post Bx, s/p transplant, stable 7 months post-transplant</td>
</tr>
<tr>
<td>Pred/CYT</td>
<td>12</td>
<td>persistent renal dysfunction (final SCr 0.8, 24h pr 4.1 g, hem)</td>
</tr>
<tr>
<td>MP/Pred/CYT/PLX/ritux</td>
<td>12</td>
<td>ESRD 3 months post Bx</td>
</tr>
<tr>
<td>Pred</td>
<td>34</td>
<td>persistent renal dysfunction (final SCr 0.6, 24h pr 2.6, no hem)</td>
</tr>
<tr>
<td>Pred/MMF</td>
<td>47</td>
<td>complete remission (final SCr 0.8, no pr, no hem)</td>
</tr>
<tr>
<td>Pred/MMF</td>
<td>52</td>
<td>persistent renal dysfunction (final SCr 2.4, 24h pr 1.5, no hem)</td>
</tr>
<tr>
<td>Pred/MMF</td>
<td>4</td>
<td>persistent renal dysfunction (final SCr 2.8, 24h pr 11, hem)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>15</td>
<td>persistent renal dysfunction (final SCr 1.3, 24h pr 3.6, hem)</td>
</tr>
<tr>
<td>Pred</td>
<td>45</td>
<td>ESRD 44 months post Bx</td>
</tr>
<tr>
<td>None</td>
<td>17</td>
<td>persistent renal dysfunction (final SCr 2.8, 24h pr 3.5, hem)</td>
</tr>
<tr>
<td>None</td>
<td>23</td>
<td>persistent renal dysfunction (final SCr 0.9, 24h pr 0.8, hem)</td>
</tr>
<tr>
<td>Pred/CYT</td>
<td>19</td>
<td>persistent renal dysfunction (final SCr 2, 24h pr 0.1)</td>
</tr>
<tr>
<td>Pred/MMF/Bort/CYT/Ritux/tacrolimus</td>
<td>41</td>
<td>ESRD 39 months post Bx</td>
</tr>
<tr>
<td>Pred</td>
<td>61</td>
<td>persistent renal dysfunction (final SCr 1.8, 24h pr 0.3, hem)</td>
</tr>
<tr>
<td>Dual/Bortizomib</td>
<td>8</td>
<td>persistent renal dysfunction (final SCr 0.7, 24h pr 0.1, hem)</td>
</tr>
</tbody>
</table>

### Clinical follow-up

- Patient received no treatment
- 17 months follow-up
  - Persistent renal dysfunction (SCr 2.8 mg/dl)
  - 3.5 grams/day proteinuria
  - Microscopic hematuria

### Why negative serum anti-GBM?

- Possible explanations:
  - Lower sensitivity of ELISA/multiplex immunoassay
  - Higher affinity of the antibodies towards GBM → deposited in the kidney rather than present in the circulation
  - Autoantibodies target GBM antigen(s) other than a3(IV)NC1
  - “Private” antigen

### Summary of differences between typical and atypical anti-GBM disease

<table>
<thead>
<tr>
<th></th>
<th>Typical anti-GBM nephritis</th>
<th>Atypical anti-GBM nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>~90% of all anti-GBM cases</td>
<td>~10% of all anti-GBM cases</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>RPGN, hematuria, mild proteinuria</td>
<td>Slowly progressive renal insufficiency, hematuria, heavy proteinuria</td>
</tr>
<tr>
<td>Lung Involvement</td>
<td>34-62%</td>
<td>Absent</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Short-lived disease</td>
<td>Indolent/chronic</td>
</tr>
<tr>
<td>Renal outcome</td>
<td>Poor (1-year survival 25%)</td>
<td>Better (1-year survival 85%)</td>
</tr>
<tr>
<td>Patient outcome</td>
<td>Guarded</td>
<td>Good (1-year survival 93%)</td>
</tr>
<tr>
<td>Serum anti-GBM antibody</td>
<td>Positive in most patients</td>
<td>Negative</td>
</tr>
<tr>
<td>Light microscopy</td>
<td>Diffuse necrotizing &amp; crescentic GN on biopsy, uninvolved glomeruli normal</td>
<td>Endocapillary, mesangial, or membranoproliferative GN with or without TMA features; absence of diffuse crescentic GN</td>
</tr>
<tr>
<td>Immunofluorescence</td>
<td>Polyclonal IF staining for IgG</td>
<td>&gt;50% show monoclonal IgG staining</td>
</tr>
</tbody>
</table>
Summary/ key points

- Atypical anti-GBM nephritis is a distinct clinicopathologic entity
- More indolent clinical course
- Unknown GBM antigen, likely different from typical anti-GBM disease

Thank you!
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