MICROSCOPIC HEMATURIA AND DIFFUSE NECROTIZING GLOMERULONEPHRITIS

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Case Presentation

• 70 years old female
• Known hypertensive on medications
• Otherwise stable
• C/O: Nausea, vomiting, fever, SOB and fluctuation of LOC progressing over two to three weeks, following URTI
• Negative symptoms:
  – No skin rashes or joint pain/swelling
  – No SOB, cough or hemoptysis
  – No chest pain, palpitations
• On examination:

PR 95/min  RR 16/min  BP 160/90  Temp 37.9 C

– she looked sick

– Respiratory examination was unremarkable.
Laboratory Workup

• Hematological workup:
  WBC 120   Hb 10.5
  PLT 586   ESR 67
  CRP 272

• Urinalysis:
  – Microscopic hematuria
  – Active sediment (WBC and red blood cell casts)
  – Mild proteinuria
Laboratory Workup

- Renal function tests:
  - Na 134
  - K 4.2
  - urea 32
  - creatinine 376 uMol/L
- 24 hour urine protein 398 mg/L/24 hours
- Serologic work-up:
  - C-ANCA 12
  - P-ANCA 6
  - Normal <5
  - C3 1.12
  - C4 0.45
  - Anti-GBM 30 (result available after biopsy)
  - Serological markers for autoimmune disease, viral hepatitis B & C, CMV, EBV, Brucella antibody all unremarkable at that time.
Renal Biopsy
Immunofluorescence

IgG
Immunofluorescence

• Four glomeruli with the following pattern:
  – IgG 3+ linear capillary wall
  – C3 2+ capillary wall
  – Negative stains: IgA, IgM, C1q and albumin.
  – No tubular basement membrane staining
Diagnosis

DIFFUSE NECROTIZING GLOMERULONEPHRITIS WITH CRESCENTS, SEE COMMENT
Follow-up

• Patient received steroids and immunosuppressive therapy. Subsequently plasmapheresis was added to the regimen.
• Patient required dialysis
• Few days later patient developed worsening of dry cough, hemoptysis and bilateral interstitial lung infiltrates
Anti-glomerular Basement Membrane Disease (Anti-GBM disease)

• Historical Perspectives:
  – In 1919, Ernest Goodpasture reported an 18 years old male with hemoptysis and acute renal failure after flu-like illness.
  – Sheer and Grossman reported linear IgG immunofluorescence in glomeruli of two patients
  – Later, Lerner established anti-GBM antibodies as a cause for pulmonary-renal syndrome and in isolated crescentic glomerulonephritis
Epidemiology

- Rare disease, 1 per 1,000,000/year in US
- Bimodal age distribution, 2\textsuperscript{nd} and 6\textsuperscript{th} decade
- No gender predilection:
  - Male predilection in 2\textsuperscript{nd} decade: pulmonary renal involvement more common
  - Female predilection in 6\textsuperscript{th} decade: often isolated crescentic GN
Frequency of Different Types of Crescentic Glomerulonephritis in Renal Biopsy Specimens Evaluated by the University of North Carolina Nephropathology Laboratory

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>Anti-GBM CGN</th>
<th>PI CGN</th>
<th>IC CGN</th>
<th>Other CGN</th>
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</thead>
<tbody>
<tr>
<td>All</td>
<td>632</td>
<td>15</td>
<td>60</td>
<td>24</td>
<td>1</td>
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<tr>
<td>1-20</td>
<td>73</td>
<td>12</td>
<td>42</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>21-60</td>
<td>303</td>
<td>15</td>
<td>48</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>61-100</td>
<td>256</td>
<td>15</td>
<td>79</td>
<td>6</td>
<td>0</td>
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</table>

Epidemiology

• In Saudi Arabia, Immune-complex-mediated GN maybe most common cause of GN

• Lupus nephritis 50% of cases
Etiology & Pathogenesis

• Multiple hits or double hits

• Autoantibody:
  – Autoantibody against NC1 domain of alpha-3 chain of Collagen (COL) IV
  – Alpha 3 chain of COL IV mapped to q35-37 region of the long arm of chromosome 2
  – Conformational changes allow formation of neo-epitopes
  – Dissociation of alpha-3 type IV collagen increased autoantibody binding affinity
Etiology & Pathogenesis

- Evidence of direct anti-GBM antibody pathogenicity:
  - Post transplant recurrence in the setting of elevated serum anti-GBM antibody
  - Correlation between antibody level and disease severity
  - De novo disease in animal models exposed to human anti-GBM
  - Elevated anti-GBM antibody prior to disease onset
Etiology & Pathogenesis

- Other immune effectors: T-cells, macrophages
- Genetic predisposition:
  - Association with HLA-DR and DQ
- Precipitating events:
  - Hydrocarbon or cigarette smoking
    - Maybe triggering event
  - Possible infections:
    - Mini-epidemics, USA and England
    - Agent?
Etiology & Pathogenesis

• Kidney transplantation for Alport syndrome:
  – Exposure to non-endogenous GBM following transplantation
  – 3-5% of Alport syndrome patients develop de novo Anti-GBM disease after transplant
Type IV collagen chain
Clinical Features

- Pulmonary hemorrhage
- Acute renal failure: rare cases with renal sparing
- Hematuria
- Proteinuria: rarely nephrotic range
Laboratory work-up

- Serum anti-GBM antibodies:
  - Different methods: ELISA, RIA immunoblot and IIFM
  - Sensitivity different methods 95-100%
  - Specificity 91-100%
  - False negative rate <5%
  - False positive rate 1%: due to antibodies directed against other types of type IV collagen
  - Low-level anti-GBM antibody titer specific to alpha3 COL IV NC1 have been reported in healthy controls.

Microscopic Features

• Cellular crescents:
  – Often >80% of glomeruli
  – Segmental fibrinoid necrosis
  – Periglomerular granulomatous inflammation or giant cells, not specific for anti-GBM
  – GBM or Bowman’s capsule BM breaks
  – Uninvolved glomerular tuft showing no features of immune complex GN (endocapillary hypercellularity, mesangial hypercellularity, wire-loops, etc…)
  – Fibrocellular or fibrous crescents are not typical
Microscopic Features

• TMA-like lesions
• Interstitial inflammation:
  – Patients with anti-tubular BM antibodies
• Necrotizing vasculitis rare
Immunofluorescence features

- Strong linear IgG >3+ staining of GBM
- Typically IgG, rarely IgA
- Linear IgG staining can be seen in diabetic patients
- 20% tubular basement membrane
Ultrastructural Features

- Non-specific
- Absent immune-complex deposition
- Breaks or disruption of GBM
Relationship Between ANCA and Anti-GBM GN (Dual Antibody CGN)

- Reports of elevated ANCA months to years prior to development of Anti-GBM disease
- 21-38% of patients of anti-GBM disease have elevated ANCA levels, usually 2/3 P-ANCA (MPO)
- Specific contribution of ANCA to Anti-GBM is unknown
- ANCA may allow surface presentation of alpha COL IV NC1 domain to antigen presentation
- Disease relapse is usually in the form of ANCA
  - Ther Apher Dial. 2009 Aug;13(4):278-81
Relationship Between ANCA and Anti-GBM GN (Dual Antibody CGN)

• Prior studies show patient with double antibodies showed more favorable course with significant renal recovery following initiating dialysis

<table>
<thead>
<tr>
<th>ANTI-GBM</th>
<th>ANCA</th>
<th>AVERAGE % OF CRESCENTS</th>
<th>RENAL SURVIVAL @ 1y</th>
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<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>72%</td>
<td>15%</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>58%</td>
<td>10%</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>45%</td>
<td>65%</td>
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ANCA-related glomerulonephritis

- Rare disease, incidence 4 Per million
- 60% of patients with CGN are ANCA positive
- Mean Age 60 years old
Pathogenesis

• Antibodies made to neutrophil lysosomal components (ANCA)
• Antibodies react to either PR3 or MPO, constituents of lysosomal proteins in neutrophils and monocytes
• ANCA-initiated signal transduction pathway of neutrophil activation, FcR participation
• Neutrophils activate alternative complement pathway
• Leukocyte activation, followed by adhesion and endothelial damage
Pathogenesis

• **Trigger:**
  - Presumed immune dysregulation
  - Evidence of molecular mimicry
  - Infection as trigger
  - Drugs: PTU, hydralazine, penicillamine, minocycline

• **Other targets:**
  - Plasminogen antibodies in 25% of ANCA positive patients
  - Anti-LAMP-2 reported in most patients with PIGN
Update on classification of ANCA-related glomerulonephritis
Renal survival in different classes

Follow up in years to renal failure

Renal survival

Focal
Crescentic
Mixed
Sclerotic

Conclusions

• Case of diffuse necrotizing glomerulonephritis with crescents, associated with C-ANCA and Anti-GBM antibodies
• Overview on Anti-GBM disease
• Literature review on relationship between ANCA and anti-GBM disease (Dual antibody CGN)
• Update on ANCA histological classification
• Questions???