Dysproteinemias, Amyloidosis, Fibrillary GN and Thrombotic Microangiopathies
Jai Radhakrishnan, MD, MS
Professor of Medicine
Columbia University

www.glomerularcenter.org

OBJECTIVES

• Dysproteinemia and Kidney Disease
• An Approach to Deposition Disease
• An Overview of Thrombotic Microangiopathy

DYSPROTEINEMIA AND KIDNEY DISEASE

Tubular Lesions in Dysproteinemia

• Tubular
  — Light Chain Cast nephropathy
  — Light Chain Fanconi's Syndrome

Myeloma Cast Nephropathy: Clinical Features

TYPICAL
  — Progressive renal insuff over 1-3 months
  — Bland sediment
  — Urine SFLC >1500mg/L
  — Dipstick negative for albumin, but positive on heat/sulfosalicylic acid
    (High UP/Creat, but low MALB/Creat)
  — Consider biopsy if above not present

OTHER
  — Hypercalcemia
  — Hyperphosphatemia and anemia out of proportion to renal failure
  — Low or positive serum anion gap

Courtesy: Glen Markowitz, MD
Plasma Exchange in Myeloma & Acute Renal Failure
A Randomized, Controlled Trial

**Results:** Composite of death, dialysis, or severely reduced kidney function (<30 ml/min) at 6 months.
- 58% with 5 - 7 plasma exchanges
- 69% with conventional therapy (P=NS)

**Limitations:**
Small study with a composite outcome (n=104)
Renal BK not used as inclusion criterion
No design for PTE to achieve pre-specified removal of LC protein.
Physicians were blinded to treatment allocation but not to treatment thereafter.


Reduction of Serum FLCs Predictive of Renal Response in MM

60% reduction in FLCs by day 21 associated with recovery of renal function for 80% of the population.


Light Chain Fanconi Syndrome (LCFS)
- Proximal tubular crystals with #1 cause of adult Fanconi syndrome
- Indolent, with "smoldering MM"
- **CLINICAL PEARL:** CKD + osteomalacia + renal glycosuria in "MGUS"

© 2013 by the American Society of Nephrology

Glomerular Lesions in Monoclonal Gammopathies

- **Organized Deposits**
  - Amyloid
  - Immunotactoid GN
  - Fibrillary GN
  - Cryoglobulinemic GN

- **Non-Organized Deposits**
  - Monoclonal Deposition disease (LC/HC/Both)
  - Proliferative GN with Monoclonal Ig Deposits
  - Intracapillary IgM deposits ("thrombi")
  - MPGN
**Clinical Presentation**

Common
- Renal insufficiency
- Proteinuria (sometimes nephrotic)
- Variable microhematuria

Unique
- Multisystem (amyloid, sometimes MIDD)
- Low complement: PGNMID, Immunotactoid

**Amyloidosis**

- Fibrillar tissue deposits that share 3 unique physicochemical properties
  - 1. Apple-green birefringence (Congo red)
  - 2. Randomly-oriented fibrils, **8-12 nm** in diameter (EM)
  - 3. Β-pleated sheet conformation
    - (X-ray crystallography or infrared spectroscopy)
    - Light chain restriction AL amyloid

**AL Amyloidosis: Clinical**

- Glomerular: Asymptomatic proteinuria-nephrosis
- Interstitial/vascular: progressive renal failure with little proteinuria
- Usually not hypertensive
- Diagnosis:
  - Fat pat 50-80 % sensitive
  - Congo Red
  - Documentation of monoclonal light chains in deposits (ALW/NAL)
  - Randomly-oriented fibrils, **8-12 nm**

**Fibrillary GN**

- Rare disorder
- 15% with monoclonal gammapathy
- Diagnosis is made by renal biopsy (EM):
  - Light Microscopy:
    - MPGN 44%
    - Mesangial proliferation 21%
    - Diffuse proliferative 15%
    - Membranous 7%
    - Diffuse sclerosis 13%
    - [Crescents 31%]
  - Immunofluorescence: IgG, kappa and lambda light chains, and C3.
  - Electron Microscopy: Mesangial and capillary wall fibrils 16 to 24 nm in diameter
Immunotactoid GN

- Clinical differences (vs. Fibrillary GN)
  - Older population
  - Association with monoclonal gammopathy 66% vs. 15%
  - Hypocomplementemia 33% vs 2%
- Mean Renal Survival 17.2 months (ESRD/Doubling)
- 3/6 pts with monoclonal gammopathy treated: 1 with CLL responded to fludarabine


MPGN with Type 2 Cryoglobulins (HCV-related)

- Organized Deposits
  - Amyloid
  - Immunotactoid GN
  - Fibrillary GN
  - Cryoglobulinemic GN
- Non-Organized Deposits
  - Monoclonal Deposition disease (LC/HC/Both)
  - Proliferative GN with Monoclonal Ig Deposits
  - Intracapillary IgM deposits (“thrombi”)
  - MPGN
Monoclonal Immunoglobulin Deposition Disease (MIDD)

- Renal parenchymal deposits of complete or partial monoclonal Ig’s (LCDD, rarely LHCDD or HCDD)
- Similar to amyloid:
  - Proteinuria +/- NS, RI
  - NSG with deposits involving all renal compartments
- Different from amyloid:
  - Granular-powdery, non-fibrillar, Congo red (-) deposits
  - Clinically significant extra-renal disease is uncommon

MIDD: Immunofluorescence

- Distribution of deposits by immunofluorescence:
  - TBMs (100%) GBMs (87%)
  - Mesangium (83%) Vessels (65%)
- LCDD
  - 90% kappa

LCDD: 63 pts from 5 centers in Northern Italy (1978-2002)

- Columbia experience (n=23)
  - Mean age 57, 52% M
  - Mean sCr 4.5
  - Mean 24 hr prot 4.2 g
  - M-spike SPEP/UPEP 87%
  - MM 39%; 90% kappa
  - Mean F/U 22.6 months
  - 48% ESRD
  - Best prognostic factor: sCr
- Northern Italy, 5 centers (65)
  - Mean age 58; 64% male
  - Mean sCr 3.8
  - Mean 24hr Uprot 2.7
  - M-spike SPEP/UPEP 94%
  - MM 65%; 68% kappa
  - Mean F/U 27.5 mos
  - 57% ESRD
  - Best prognostic factors
    - MM, age, sCr
  - 35% extra-renal sympt
    - Mainly heart / liver
"Proliferative GN with Monoclonal Ig Deposits"

- Proliferative GN
- Deposits with LC restriction
- Granular, non-fibrillar, Congo red (-)
- No evidence of cryoglobulinemia (37/37)

Monoclonal IgM Deposits

- Intracapillary IgM deposits "thrombi" should suggest Waldenstrom’s Disease

Spectrum of IgM Monoclonal Dz -GN

- 14 pts: 7 with nephrosis, 14 with CKD
- Monoclonal IgM preceded kidney dz by 29 M
  - 7: Waldenström’s
  - 7: B Cell lymphoma, Myeloma, IgM-related disorder
- Pathology:
  - Intracapillary deposits
  - MPGN
  - Amyloid
  - Infiltrative
  - ATN
- Course/Prognosis: Improvement after chemotherapy

PGNMID: Clinical

- Clinical Presentation
  - mean age 54.5 yrs
  - CKD: mean sCr 2.77 mg/dl
  - Proteinuria: mean prot 5.7 g/day; 48.6% full NS
  - microhematuria 77.1%
  - hypocomplementemia 27% (10/37)
  - M-spike 27% (10/37)

- BM bx in 22 pts (including 9/10 w/M-spike):
  - 1 = MM (known hx); 1 = 5% plasma cells w/lambda restriction; 20 = <5% plasmacytosis
  - Follow-up avail 32 pts; mean 30.3 months
  - 37.5% CR/PR; 37.5% PRD; 21.9% ESRD
  - Rx widely varying; immunosuppression in 56.3% (ritux = 4)
  - Only 1 of 27 subsequently developed M-spike
  - None subsequently developed MM or lymphoma
  - Thus only 1/37 with MM; none with lymphoma

PGNMID: Clinical Presentation

- mean age 54.5 yrs
- CKD: mean sCr 2.77 mg/dl
- Proteinuria: mean prot 5.7 g/day; 48.6% full NS
- microhematuria 77.1%
- hypocomplementemia 27% (10/37)
- M-spike 27% (10/37)
“MPGN secondary to monoclonal gammopathy”

28 of 68 HBV/HCV pts (41.1%) with MPGN @ Mayo clinic found to have a monoclonal gammopathy
• BM Bx: 16 "MGUS"; 6 MM; 5 low-grade lymphoma, 1 Lymphoblastic lymphoma w/Waldenstrom’s MG

Dysproteinemia-Associated Renal Disease: Other Lesions

Pamidronate: Collapsing FSGS
Zoledronate: ATN

Workup for suspected Monoclonal Gammopathy

• Serum protein electrophoresis with immunofixation (false neg 6.5%)
• 24-h urine electrophoresis
• Serum Free light chains could replace urine electrophoresis
• Suspect amyloid: Do all three

International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders

Myeloma and the Kidney
Renal manifestation in MM

<table>
<thead>
<tr>
<th>Renal manifestation/histological feature</th>
<th>Typical clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cast nephropathy</td>
<td>Hyaline fractured casts, degenerated tubular cells</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>Fibril; Congo red +ve</td>
</tr>
<tr>
<td>LCDD/HCDD</td>
<td>Deposition of light or heavy chains</td>
</tr>
<tr>
<td>Tubular disturbance</td>
<td>Fanconi syndrome, proximal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td>Hyaline fractured casts, degenerated tubular cells</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>Fibril; Congo red +ve</td>
</tr>
<tr>
<td>LCDD/HCDD</td>
<td>Deposition of light or heavy chains</td>
</tr>
<tr>
<td>Tubular disturbance</td>
<td>Fanconi syndrome, proximal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td>Hyaline fractured casts, degenerated tubular cells</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>Fibril; Congo red +ve</td>
</tr>
<tr>
<td>LCDD/HCDD</td>
<td>Deposition of light or heavy chains</td>
</tr>
<tr>
<td>Tubular disturbance</td>
<td>Fanconi syndrome, proximal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td>Hyaline fractured casts, degenerated tubular cells</td>
</tr>
</tbody>
</table>

HUS

**Primary** TMA

<table>
<thead>
<tr>
<th>HUS</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td><strong>Mechanisms</strong></td>
</tr>
<tr>
<td>1. Thrombocytopenia</td>
<td>STEC-HUS: Shiga toxin producing E. coli</td>
</tr>
<tr>
<td>2. MAHA</td>
<td>Alternative complement disorders</td>
</tr>
<tr>
<td>3. Renal involvement</td>
<td>ADAMTS-13 abnormalities</td>
</tr>
<tr>
<td>(30% have CNS involvement and fever)</td>
<td></td>
</tr>
<tr>
<td>4. Fever</td>
<td></td>
</tr>
<tr>
<td>5. CNS involvement (3% with the &quot;pentad&quot;)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
</table>

Secondary TMA

- Pregnancy (Pre-Eclampsia-HELLP)
- Malignant HTN
- Systemic sclerosis
- Infections e.g. HIV
- Autoimmune disease (e.g. SLE)
- Disseminated malignancy
- Stem cell transplant
- Anti Phospholipid Syndrome
- Drugs: calcineurin inhibitors, quinine, antiplt agents (ticlodipine), chemotherapy (mitomycin, gemcitabine, VEGF inhibitors)
**STEC-HUS**

- Typically in young patients.
- HUS in 6-9% of infected children
- Enterohemorrhagic E Coli (O157:H7, O104:H4), S dysenteriae
- Bloody diarrhea prodrome 5-10 days
- 60% dialysis, mean time on dialysis: 10 d.
- 25% with neurological symptoms
- 4% mortality
- 5-25% with long term morbidity (HTN, proteinuria, decreased GFR)


**STEC-HUS: Pathogenesis**


**STEC-HUS: Management**

- **Supportive care**
  - PRBC when Hb < 6g/dL
  - CCB for HTN
  - dialysis
- **CNS involvement**
  - (Plasma exchange)
  - (Eculizumab)
- **Not useful**
  - Shiga toxin binding agents
- **Harmful**
  - Antibiotics
  - Anti-motility agents
  - Urokinase, heparin, dipyridamole

**Atypical HUS**

- 10–15 % of patients with HUS
- Poor long-term prognosis and disease recurrence is common.
- Can lead to ESKD.
- Often associated with complement deregulation caused by mutations of complement components and regulators.

Upon activation of the alternative pathway C3 is cleaved by the C3 convertase to C3b with deposits on target cells.

Factor H inhibits the activity of the reaction at the cell surface.

Factor I is a serine protease that cleaves C3b to inactive C3b.

MCP acts as a cofactor for factor I-mediated cleavage of C3b to inactive C3b.

aHUS: Response to PLEX and Outcome

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>ESR or Death (5 years)</th>
<th>Response to Plasma (instability of episode + C3 or HC Total of twice episodes)</th>
<th>Good Kidney Transplantation</th>
<th>Outcome at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>49 (77%)</td>
<td>57 (50%)</td>
<td>5 (29%)</td>
<td></td>
</tr>
<tr>
<td>CFI</td>
<td>64 (46%)</td>
<td>2 (2%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>THBD</td>
<td>7 (54%)</td>
<td>7 (54%)</td>
<td>7 (54%)</td>
<td></td>
</tr>
<tr>
<td>MCP</td>
<td>1 (8%)</td>
<td>10 (75%)</td>
<td>3 (25%)</td>
<td></td>
</tr>
<tr>
<td>CFH Ab</td>
<td>9 (10%)</td>
<td>9 (10%)</td>
<td>9 (10%)</td>
<td></td>
</tr>
<tr>
<td>Non acute</td>
<td>4 (50%)</td>
<td>71 (60%)</td>
<td>12 (12%)</td>
<td></td>
</tr>
<tr>
<td>Sporadic</td>
<td>85 (40%)</td>
<td>136 (89%)</td>
<td>19 (8%)</td>
<td></td>
</tr>
<tr>
<td>Paediatric</td>
<td>53 (54%)</td>
<td>43 (80%)</td>
<td>7 (80%)</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>70 (44%)</td>
<td>11 (70%)</td>
<td>8 (70%)</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>43 (60%)</td>
<td>51 (50%)</td>
<td>16 (40%)</td>
<td></td>
</tr>
</tbody>
</table>

Eculizumab in aHUS

<table>
<thead>
<tr>
<th>Complement Cascade</th>
<th>Eculizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3b</td>
<td>x C5b</td>
</tr>
<tr>
<td>x C5b-9</td>
<td>x C5b-9</td>
</tr>
</tbody>
</table>

Primary Endpoint: Change in Platelet Count

Change in Platelet Count P=0.0001
Mean Change From Baseline at Week 26: 96 ± 21 x10^11/L

- 77% (13/17) of patients achieved platelet normalization

Secondary Endpoint: Change in CKD Stage

65% Improved ≥ 1 CKD Stage (95% CI 33-82)

- 88% (15/17) improved eGFR
  - 11 improved eGFR ≥ 1 CKD stage
  - 4 improved eGFR < 1 CKD stage

- 5/7 dialysis patients became dialysis-free
Eculizumab Was Well Tolerated

- No meningococcal infection
- Most common adverse event as reported by Investigators:
  - Anemia (35%; 1 severe),
  - Headache (41%; 1 severe)
  - Diarrhea (35%)
  - Vomiting (29%)
  - Nausea (24%)
- 1 patient withdrawal due to adverse event deemed unrelated to drug
  - Worsening of pancytopenia (patient on Azathioprine)

TTP

- Among patients with ADAMTS13 activity <5%
  - Median age 40
  - Age-sex-race incidence rate ratio
    - Black/Non-Black 9.3
    - Women/Men 2.7
- Incidence 3-10 per 10⁶
- The incidence of non-idiopathic TTP appears to be much higher, but difficult to determine accurately. (e.g.; ~ 5% of patients with disseminated malignancy?)

ADAMTS-13 and TTP

ADAMTS 13 Mutations

Antibodies to ADAMTS 13

- Autoantibody inhibitors are reported in 30 - 95% of patients with idiopathic TTP.
- IgG antibody is detected in almost all patients with idiopathic TTP and severe ADAMTS13 deficiency.
- IgM Ab also detected in 11% of patients.
TTP therapy: Plasma Exchange (PEX)

- Daily PEX (1–1.5 plasma volume with fresh frozen plasma or cryo-poor plasma).
- PEX continued until the platelet count (>150K) and hemolysis markers normalize.
- ~20% of patients show a minimal or transient response to initial plasma exchange.

Role of Adjuvant Therapy in TTP

- Corticosteroids:
  - Severe ADAMTS 13 deficiency (<10%)
- Rituximab:
  - Complicated/severe initial episode and relapses
- Cyclosporine:
  - (similar indications as rituximab)
- Cyclophosphamide & Vincristine:
  - Refractory to above
- Splenectomy:
  - Refractory to above

Summary

TMA

- aHUS
- TTP
- STEC-HUS
- Secondary

Supportive Care

Plasma Exchange

TTP: Immunosupp.

aHUS: eculizumab

Support Treat Primary Disease

PLEX considered *

* PLEX Not Useful
  - Stem Cell
  - Malignancy
  - Mitomycin

Kidney International (2009) 75 (Suppl 112), S55–S58