Dysproteinemias, Amyloidosis, Fibrillary GN and Thrombotic Microangiopathies

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OBJECTIVES

• PART 1
  – Dysproteinemia and Kidney Disease

• PART 2
  – An Overview of Thrombotic Microangiopathy

DYSPROTEINEMIA AND KIDNEY DISEASE

Recapitulating Monoclonal Kidney Disease in a Mouse Model

Tubular Lesions in Dysproteinemia

- **Tubular**
  - Light Chain Cast nephropathy
  - Light Chain Fanconi’s Syndrome

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**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

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Treatment of Myeloma

- Candidate for Autologous Stem Cell Transplant?
- Common Protocols in Use
  - Bortezomib (Velcade) plus cyclophosphamide and dexamethasone (VCD or CyBorD)
  - Lenalidomide (Revlimid) plus dexamethasone (Rd)
  - Bortezomib (Velcade) plus melphalan and prednisone (VMP)
  - Melphalan plus prednisone and thalidomide (MPT)
  - Thalidomide plus dexamethasone (Td)
  - Bortezomib (Velcade) plus lenalidomide (Revlimid) and dexamethasone (VRd)

Blood. 2011 Jun 9;117(23):6063-73

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.


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 BX 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.


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"

Courtesy: Glen Markowitz, MD
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 of Glomerular Disease associated with Monoclonal Gammopathy

**Common**
• Renal insufficiency
• Proteinuria (sometimes nephrotic)
• Variable microhematuria

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

Treatment Principles

• Treatment is directed at the abnormal clone
• Evidence-based strategies do not exist

AL Amyloidosis: Clinical

• Glomerular:
  Asymptomatic proteinuria to frank nephrosis
• Interstitial/vascular: progressive renal failure with little proteinuria
• Usually not hypertensive
• Diagnosis is made by biopsy:
Fat Pad Biopsy

[Image: Fat Pad Biopsy graph]

[Image: Fat Pad Biopsy microscopy]

Renal Biopsy

Amorphous material weakly PAS +ve
Congo Red: Apple green birefringence on polarizing microscopy

Typing Amyloid

1. Congo Red positive, EM 10-12 nm
2. Immunofluorescence
   - Kappa/lambda/heavy chain restricted: AL/AH amyloid
   - AA protein: AA amyloid
   - [OTHERS: AFib, ATTR, AApoA1, and AB2m]
3. Proteomic Analysis:
   Laser Capture Microdissection
   -> Mass Spect

[Image: Renal Biopsy microscopy]

[Image: Amyloid typing]

Blood. 2012 Oct 18;120(16):3206-13
Treatment Approach to AL Amyloidosis

- Autologous hematopoietic cell transplantation (HCT) eligible
  - Melphalan -> HCT -> sFLC reduction -> Bortezomib in high risk patients
- HCT ineligible
  - CyBorD: cyclophosphamide, bortezomib, and dexamethasone or Melphalan/dexamethasone

Fibrillary GN

- Rare disorder
- 15% with monoclonal gammopathy
- 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


Stem Cell Transplant:
sFLC Response Predicts Outcome

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


Immunotactoid GN

<table>
<thead>
<tr>
<th>MPGN</th>
<th>DPGN</th>
<th>+ Membranous</th>
<th>2/3 Monoclonal</th>
</tr>
</thead>
</table>

Fibrillary
15-30 nm

Immunotactoid
30-90 nm

MPGN with Type 2 Cryoglobulins (HCV-related)

30-40 nanometer

Courtesy: Glen Markowitz, MD
Glomerular Lesions in Monoclonal Gammopathies

- **Organized Deposits**
  - Amyloid (10nm)
  - Immunotactoid GN (40nm)
  - Fibrillary GN (20nm)
  - Cryoglobulinemic GN (30nm)

- **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
  - LHCDD (rare)
  - HCD (rare)

- Extrarenal disease (cardiac, pulmonary, liver) may be seen

- Granular-powdery, non-fibrillar, Congo red NEGATIVE deposits

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Differential Diagnosis of Nodular Glomerulosclerosis

<table>
<thead>
<tr>
<th>Entity</th>
<th>LM</th>
<th>IF</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic nodular glomerulosclerosis</td>
<td>Nodules more frequent and isometric than DM</td>
<td>Negative</td>
<td>Five fibrils in matrix, but no deposits</td>
</tr>
<tr>
<td>Nodular diabetic glomerulosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesangial deposits</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPGN</td>
<td>Double contours and cellular</td>
<td>and/or C3</td>
<td>Granular deposits</td>
</tr>
<tr>
<td>Amyloidosis (AA)</td>
<td>Congo red positive</td>
<td>Monoclonal light chain is 4k</td>
<td>Random non-branching fibrils (8-12 nm)</td>
</tr>
<tr>
<td>Monoclonal lg deposition disease</td>
<td>Nodules more uniform than DM and less cells; no Extra</td>
<td>Negative</td>
<td>Monoclonal light chain and/or heavy chain</td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis</td>
<td>Congo red negative</td>
<td>Functional IgG and C3</td>
<td>Fibrils (16-24 nm)</td>
</tr>
<tr>
<td>Immunotactoid glomerulonephritis</td>
<td>Congo red negative</td>
<td>Monoclonal light and/or heavy chain</td>
<td>Microtubules (20-50 nm)</td>
</tr>
<tr>
<td>Type III collagen glomerulopathy</td>
<td>Mesangial deposits are IgG positive but Jones negative</td>
<td>Negative</td>
<td>Massive electron-dense deposits (mostly amorphous) replacing mesangial matrix; GBM of normal thickness</td>
</tr>
<tr>
<td>Type III collagen glomerulopathy</td>
<td>May be hypercellular</td>
<td>Negative</td>
<td>Fibrins with characteristic 60-nm periodicity</td>
</tr>
</tbody>
</table>

Kidney International (2012) 82, 1141–1142;
Immunofluorescence:
- TBM (100%)
- GBM (87%)
- Mesangium (83%)
- Vessels (65%)
- Light Chain restriction 90% kappa

**MIDD: Electron Microscopy**

Inconstant electron-dense, subendothelial, granular, punctate deposits that may diffusely infiltrate the basal lamina.

**“Proliferative GN with Monoclonal Ig Deposits”**

- Proliferative GN
- Deposits with LC restriction, IgG3-K
- Deposits with IgG subclass restriction
- Granular, non-fibrillar, Congo red (-)
- No evidence of cryoglobulinemia (37/37)

**PGNMID: Clinical**

- Clinical Presentation
  - CKD, variable proteinuria, hematuria hypocomplementemia 27% (10/37)
  - M-spike 27% (10/37)
  - BM Bx usually normal
  - Treatment unknown
- Follow-up:
  - Progressive CKD/ESRD
  - None developed MM or lymphoma

Nasr S. J Am Soc Nephrol. 2009 Sep;20(9):2055-64
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: Waldenstrom’s
  - 7: B Cell lymphoma, Myeloma, IgM-related disorder
- Pathology:
  - Intracapillary deposits
  - MPGN
  - Amyloid
  - Infiltrative
  - ATN
- Course/Prognosis: Improvement after chemotherapy

“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

CLL-related GN

- 5/13: MPGN with cryoglobulins(Type I or II)
- 2/13: MPGN/MesPGN without cryo (monoclonal deposits)
- 2/13: MGN/MPGN with Monoclonal Fibrillary deposits

Chlorambucil produced complete remission of NS and improved/stabilized GFR in 5/5 pts

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

Leukemia. 2009 Feb;23(2):215-24

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>Fibrils, 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, Hyperaminaciduria, glucosuria</td>
</tr>
<tr>
<td>Renal insufficiency caused by</td>
<td>Proximal tubular acidosis, Acidosis</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>High plasma calcium</td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>Increased plasma monoclonal IgM</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>Hyperuricemia, (high tumour load)</td>
</tr>
<tr>
<td>MPGN</td>
<td>Cryoglobulins</td>
</tr>
<tr>
<td>Plasma cell infiltrates</td>
<td>Direct infiltrates</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Light-chain deposition in the muscle</td>
</tr>
<tr>
<td>Pyelonephritis/sepsis</td>
<td>Immunodeficiency with frequent infections</td>
</tr>
</tbody>
</table>


THROMBOTIC MICROANGIOPATHY
Chronic Uncontrolled Complement Activation Leads to Endothelial and End Organ Damage

Clinical Consequences:
- Platelet consumption
- Mechanical hemolysis
- Blood clotting
- Vessel occlusion
- Inflammation
- Ischemia
- Systemic multi-organ complications

Fibrin deposition in microvasculature:
- Microangiopathic hemolytic anemia (MAHA)
- Thrombocytopenia <150,000 or >25% from baseline
- Organ dysfunction >1 of:
  - Neurological
  - Renal
  - GI
  (Normal PT/PTT)

Secondary TMA
- 1) Connective Tissue Disease (SLE, scleroderma)
  - +/- Antiphospholipid Ab Syndrome
- 2) Drug associated
  - calcineurin inhibitors, quinine, antiplt agents (ticlodipine), chemotherapy (mitomycin, gemcitabine, VEGF inhibitors)
- 3) Infectious e.g. pneumococcus
- 4) Pregnancy
- 5) Disseminated Malignancy
- 6) Stem Cell Transplant
- 7) Malignant Hypertension
- 8) Pancreatitis

Thrombotic microangiopathy
- • Fibrin deposition in microvasculature:
  - Microangiopathic hemolytic anemia (MAHA)
  - Thrombocytopenia <150,000 or >25% from baseline
  - Organ dysfunction >1 of:
    - Neurological
    - Renal
    - GI
    (Normal PT/PTT)

STEP 2: “Primary” TMA:
- Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP)

<table>
<thead>
<tr>
<th>HUS</th>
<th>TTP</th>
</tr>
</thead>
</table>
| **Mechanisms** | STEC-HUS: Shiga toxin
aHUS: Alternative complement disorders |
| **Age** | Children |
| **Clinical features** | MAHA
1- MAHA
2- Thrombocytopenia
3- Renal involvement
(30% have CNS involvement and fever) |
| **Mechanisms** | ADAMTS-13 abnormalities |
| **Age** | Adults |
| **Clinical features** | MAHA
1- MAHA
2- Thrombocytopenia <20K
3- Mild renal involvement
4- CNS involvement
5- Fever
(3% with the “pentad”) |

George JN. H Blood 2010;116:4060-4069
TTP

- Among patients with ADAMTS13 activity <5%
  - Median age 40
- Incidence 3-10 per 10^6
- Thrombocytopenia and CNS symptoms predominate. TTP UNLIKELY IF
  - Serum creatinine >200 µmol/l (2.2mg/dL)
  - Minimum Platelets >30,000/mm³

George JN Kidney Int 2009; 75: S8-S10

TTP therapy: Plasma Exchange (PLEX)

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

Kidney International (2009) 75 (Suppl 112), S55–S58
Role of Adjuvant Therapy in TTP

- **Corticosteroids:**
  - Severe ADAMTS 13 deficiency (<10%)  
  
- **Rituximab or Cyclosporine:**
  - Complicated/severe initial episode and relapses

- **Cyclophosphamide & Vincristine:**
  - Refractory to above

- **Splenectomy:**
  - Refractory to above

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**STEC-HUS**

- Young patients.
  - 6–9% of STEC infected children have HUS
- 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)

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**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.

Complement Pathway Activation and Control

- Classical pathway
  - Components C1 – C4
- Amplification loop
  - C3 activation
- Autoactivation of C3, and factors B and D
- Alternative pathway
  - Factor B
  - Factor D
  - C3

Eculizumab
  - (anti C5 mAb)
  - Inhibited by FH, FI, CD46

Generation of the membrane attack complex resulting in cell lysis

aHUS and Genetic Complement Abnormalities

Factors That Amplify Complement Activation

Treatment of aHUS

- Start plasma exchange in all patients!
- Maintenance
- Plasma exchange
- Plasma infusion if factor deficiency
- Immunosuppr if Ab to complement inhibitory proteins: e.g. MMF/steroids/rituximab
- Terminal Complement inhibitors
  - Eculizumab

Eculizumab in aHUS

Primary Endpoint: Change in Platelet Count

Change in Platelet Count $P<0.0001$

Mean Change From Baseline at Week 26: $96 \pm 21 \times 10^9/L$

- Immediate and sustained increase in platelets
- 77% (13/17) of patients achieved platelet normalization
Secondary End Point: 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

ARS Case history: 46 F

- Oct 2007: Nausea, wt gain, BP 220/140
  Creatinine 4.0 mg/dL, Hb 8.9, Plt 46 K.
  Some schistocytes on peripheral smear.
  UA 10 RBC/HPF, UP/C 2.3
  Renal USG normal sized, echogenic kidneys
  — Blood pressure improved with calcium blockers
  and diuretics 150/90 mmHg, Plts improved to
  100K, Scr 2.8mg/dL, discharged home

ARS: What is your next step?

- Start TMA workup
- Start plasma exchange
- Optimize antihypertensives, ESRD planning
- Eculizumab

Recurrence of symptoms and headache (on anti HTN meds). + Seizures
BP 160/110. + retinal hge. Head CT: PRES
Laboratory
- Serum Cr 6.9 mg/dL,
- Hb 6.9, plt 93 K, +schistocytes
- LDH 622 (<221) U/L
- Urinalysis 3+ blood and 2+ protein
- 24 hour urine protein 4 g
- Negative ANA, anti-DNA antibody, and ANCA
- Normal C3 and C4
Approach to this Case of TMA

- Start plasma exchange
- Secondary TMA analysis:
  - Malignant hypertension (unlikely since BP levels did not correlate with TMA; HTN likely a result)
- STEC-HUS analysis: No history of preceding diarrhea and relapsing course
- TTP analysis: ADAMTS13 levels were normal

Likely aHUS

Summary

**TMA**
- aHUS
  - TTP
- STEC-HUS
  - Secondary

Plasma Exchange
Supportive Care
Treat Primary Disease

aHUS: eculizumab
TTP: immunosupp.

PLEX considered *

*PLEX Not Useful:
  - Stem Cell
  - Malignancy
  - Mitomycin

END