Monoclonal Gammopathies of Renal Significance

Nelson Leung, MD
March 21st – 22nd, 2014
Disclosure

• None
Objectives

- Define the entity “monoclonal gammopathy of renal significance (MGRS)”
- Review the complications of MGRS
- Review the diagnosis of MGRS
- Explore treatment options of MGRS
Case #1

• 51 yo previously healthy Royal Canadian Mounted Police
  • 2 year history of
    • Arthralgias
    • Fatigue
    • Vasculitic rash – biopsy suggests cryoglobulinemia
    • Cryoglobulins were negative
  • Presented in February
    • Shortness of breathe
    • Acute renal failure
      • Creatinine = 4.1 mg/dL
    • Renal biopsy was obtained
Crystalline IgGκ thrombi with periodicity
Case cont.

• “Glomerulopathy of monoclonal gammopathy of undetermined significance”
  • Cryoglobulins were repeated and was negative
  • SPEP was negative

• Patient was treated with high dose corticosteroids

• Renal function improved to creatinine 1.9 mg/dL
Clinical course

• 2 year later in February
  • Sudden onset of dark urine and anuria
  • Angiogram showed small vessel occlusions
  • No response to TPA
Laboratory Values

- Hemoglobin – 14.3 g/dL
- Platelet – 12,000 x 10^6/L
- Creatinine - 8.2 mg/dL
- LDH – 1253 U/L
- C3 - 0.78 g/L (normal 0.9 – 1.8 g/L)
- C4 – normal, ANA, ANCA, ENA - negative
- Cryoglobulins were again negative
Further Evaluation

• Ca – 9.7 mg/dL
• Cryoglobulins were negative
• Immunofixation – small monoclonal IgG<sub>κ</sub>
  • M-spike – 0.4 g/dL
  • BM showed 1% plasma cells
  • Bone survey showed no lytic lesions
Case Report

A case of bilateral renal arterial thrombosis associated with cryocrystalglobulinaemia

Nelson Leung¹, Francis K. Buadi², Kevin W. Song³, Alexander B. Magil⁴ and Lynn D. Cornell⁵

- Usually associated with multiple myeloma
- Thrombosis most often occur in the periphery
- Central thrombosis have only been reported in fulminant end stage myeloma patients
Questions

1. Does this patient have multiple myeloma?

2. Should this patient receive treatment?
   a) What type of treatment should he receive?
   b) Is multiple myeloma necessary for initiation of treatment?
   c) Can myeloma therapy be used if multiple myeloma is not present?

3. Are there severe consequences if no treatment is offered?
## Diagnostic Criteria of Plasma Cell Dyscrasias

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-spike</td>
<td>&lt; 3 g/dL</td>
<td>≥ 3 g/dL</td>
<td>≥ 3 g/dL</td>
</tr>
<tr>
<td>Bone Marrow PC</td>
<td>&lt; 10%</td>
<td>≥ 10%</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>Hypercalcemia (C)</td>
<td>absent</td>
<td>absent</td>
<td>+/-</td>
</tr>
<tr>
<td>Renal impairment (R)</td>
<td>absent</td>
<td>absent</td>
<td>+/-</td>
</tr>
<tr>
<td>Anemia (A)</td>
<td>absent</td>
<td>absent</td>
<td>+/-</td>
</tr>
<tr>
<td>Lytic lesions (B)</td>
<td>absent</td>
<td>absent</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Renal impairment is defined by a serum creatinine > 2 mg/dl in which the injury is associated with the plasma cell disorder.

Kyle et al. Leukemia 2010
Talamo et al. Clin Lymphoma, Myeloma & Leukemia. 2010
Questions

1. Does this patient have multiple myeloma?

2. Should this patient receive treatment?
   a) What type of treatment should he receive?
   b) Is multiple myeloma necessary for initiation of treatment?
   c) Can myeloma therapy be used if multiple myeloma is not present?

3. Are there severe consequences if no treatment is offered?
Patients with smoldering myeloma with FLC ratio <0.125 or >8 plus X10% plasma cells in the marrow are at high risk of progression in the first 2 years following recognition. These patients should be considered candidates for chemoprevention trials.”

“However, off-study, observation is still the standard even in this group.”
Reasons for not treating SMM(MGUS)

• Lack of benefits from most clinical trials
  • Melphalan & prednisone
  • Thalidomide with or without bisphosphonate
  • Lenalidomide*

• Risk of myelodysplasia and secondary malignancies from alkalytor based therapy
Prognostication models for progression of smoldering multiple myeloma

Dispenzieri et al. Blood 2014
Questions

1. Does this patient have multiple myeloma?

2. Should this patient receive treatment?
   a) What type of treatment should he receive?
   b) Is multiple myeloma necessary for initiation of treatment?
   c) Can myeloma therapy be used if multiple myeloma is not present?

3. Are there severe consequences if no treatment is offered?
Monoclonal Immunoglobulin Deposition Disease

- LCDD
- HCDD
- LHCDD
MIDD and Lymphoproliferative disorders

- **Malignancies**
  - 65% meet criteria for multiple myeloma
  - 3% - chronic lymphocytic lymphoma
  - 32% - “idiopathic”
Patient and Renal Survival in LCDD

Long-Term Outcome of Renal Transplantation in Light-Chain Deposition Disease

Nelson Leung, MD, Donna J. Lager, MD, Morie A. Gertz, MD, Kirk Wilson, Sharan Kanakiriya, MD, and Fernando C. Fervenza, MD
Proliferative Glomerulonephritis with Monoclonal IgG Deposits

Samih H. Nasr,* Anjali Satoskar,† Glen S. Markowitz,* Anthony M. Valeri,‡ Gerald B. Appel, † Michael B. Stokes,* Tibor Nadasdy, † and Vivette D. D’Agati*
Monoclonal Protein Characteristics of PGNMID

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG^a</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>IgG1 κ</td>
<td>7/32</td>
<td>21.9</td>
</tr>
<tr>
<td>IgG1 λ</td>
<td>2/32</td>
<td>6.3</td>
</tr>
<tr>
<td>IgG2 λ</td>
<td>2/32</td>
<td>6.3</td>
</tr>
<tr>
<td>IgG3 κ</td>
<td>17/32</td>
<td>53.1</td>
</tr>
<tr>
<td>IgG3 λ</td>
<td>4/32</td>
<td>12.5</td>
</tr>
<tr>
<td>C3</td>
<td>36</td>
<td>97.3</td>
</tr>
<tr>
<td>C1q</td>
<td>23/36</td>
<td>63.9</td>
</tr>
</tbody>
</table>

Evidence of dysproteinemia (n [%])
- Serum paraprotein only: 4 (11.5%)
- Serum and urine paraprotein: 7 (18.9%)
- Multiple myeloma: 1 (2.7%)
- AL-amyloid: 1 (2.7%)
- Low C3 (n [%]): 3 (8.1%)
- Low C4 (n [%]): 3 (8.1%)
- Low C3 and C4 (n [%]): 4 (10.8%)
- Positive serum cryoglobulin (n [%]): 0 (0.0%)
- Positive hepatitis C antibody (n [%]): 1/30 (3.3%)
- Positive rheumatoid factor (n [%]): 1/18 (5.5%)
# Outcomes of Patients with PGNMID

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up (mo; mean [range])</td>
<td>30.3 (1.0 to 114.0)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>RAS blockade alone</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>IM</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>steroids</td>
<td>11</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>3</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>2</td>
</tr>
<tr>
<td>mycophenolate mofetil</td>
<td>5</td>
</tr>
<tr>
<td>rituximab</td>
<td>4</td>
</tr>
<tr>
<td>chlorambucil</td>
<td>1</td>
</tr>
<tr>
<td>thalidomide</td>
<td>2</td>
</tr>
<tr>
<td>bortezomib (Velcade)</td>
<td>1</td>
</tr>
<tr>
<td>Outcome&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>PR</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>PRD</td>
<td>12 (37.5)</td>
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<tr>
<td>Persistent hematuria (with normal creatinine and no proteinuria)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>ESRD</td>
<td>7 (21.9)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (15.6)</td>
</tr>
</tbody>
</table>
# Proliferative Glomerulonephritis with Monoclonal IgG Deposits Recurs in the Allograft

Samih H. Nasr,* Sanjeev Sethi,* Lynn D. Cornell,* Mary E. Fidler,* Mark Boelkins,† Fernando C. Fervenza,‡ Fernando G. Cosio,§ and Vivette D. D’Agati§

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplant</td>
<td>57</td>
<td>62</td>
<td>75</td>
<td>40</td>
</tr>
<tr>
<td>Kidney source</td>
<td>Living-unrelated donor</td>
<td>Deceased donor</td>
<td>Living-related donor</td>
<td>Living-unrelated donor</td>
</tr>
<tr>
<td>HLA mismatch</td>
<td>4 of 6 HLA antigens</td>
<td>0 of 6 HLA antigens</td>
<td>2 of 6 HLA antigens</td>
<td>4 of 6 HLA antigens</td>
</tr>
<tr>
<td>Percent PRA*</td>
<td>1% for class I</td>
<td>0% for class I</td>
<td>0% for class I</td>
<td>0% for class I</td>
</tr>
<tr>
<td>Maintenance immunosuppressive regimen</td>
<td>FK506/PRED/MMF</td>
<td>FK506/PRED/Myfortic acid</td>
<td>FK506/PRED/MMF</td>
<td>FK506/PRED/MMF</td>
</tr>
<tr>
<td>Time from transplant to diagnosis of recurrent disease</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Baseline serum creatinine (mg/dl)</td>
<td>1.9</td>
<td>1.2</td>
<td>1.4</td>
<td>0.9</td>
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<tr>
<td>Parameters at the time of first biopsy showing recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum creatinine (mg/dl)</td>
<td>2.8</td>
<td>3.7</td>
<td>4.8</td>
<td>1.2</td>
</tr>
<tr>
<td>24-hour urine protein serum albumin</td>
<td>0.790</td>
<td>7.4</td>
<td>5.8</td>
<td>0.061</td>
</tr>
<tr>
<td>serum albumin</td>
<td>3.5</td>
<td>2.0</td>
<td>3</td>
<td>4.4</td>
</tr>
</tbody>
</table>
Recurrent membranoproliferative glomerulonephritis after kidney transplantation

Elizabeth C. Lorenz¹, Sanjeev Sethi², Nelson Leung¹, Angela Dispenzieri³, Fernando C. Fervenza¹ and Fernando G. Cosio¹,⁴

![Graph showing proportion of patients with recurrent MPGN over months of recurrence.](graph1.png)

![Graph showing complement levels and rMPGN over months post-transplant.](graph2.png)

![Graph showing serum monoclonal proteins and rMPGN over months post-transplant.](graph3.png)

- **Graph 1:** Proportion of patients with recurrent MPGN over months of recurrence.
  - **Graph 2:** Proportion of patients with rMPGN over months post-transplant.
  - **Graph 3:** Serum monoclonal proteins and rMPGN over months post-transplant.

*P = 0.02*

*P = 0.08*
Recurrence and Graft Survival with and without MG in Fibrillary Glomerulonephritis

P=0.10

P=0.24
Questions

1. Does this patient have multiple myeloma? **NO**

2. Should this patient receive treatment?
   a) Is multiple myeloma necessary for initiation of treatment?
   b) Should he receive myeloma therapy if he does not have multiple myeloma?

3. Will there be severe consequences if no treatment is offered? **YES**
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<tr>
<td>Lytic lesions (B)</td>
<td>absent</td>
<td>absent</td>
<td>+/-</td>
</tr>
</tbody>
</table>

1. PC > 10% + cast nephropathy?
2. PC > 10% + membranoproliferative glomerulonephritis with a Scr < 2 mg/dl?
3. PC < 10% + PGNMID?

Kyle et al. Leukemia 2010
Talamo et al. Clin Lymphoma, Myeloma & Leukemia. 2010
Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

Nelson Leung, Frank Bridoux, Colin A. Hutchison, Samih H. Nasr, Paul Cockwell, Jean-Paul Fermand, Angela Dispenzieri, Kevin W. Song and Robert A. Kyle
Dangerous small B-cell clones

Giampaolo Merlini and Marvin J. Stone
NEPHROTOXIC POTENTIAL OF BENCE JONES PROTEINS — SOLOMON ET AL.

NEPHROTOXIC POTENTIAL OF BENCE JONES PROTEINS

Alan Solomon, M.D., Deborah T. Weiss, B.S., and Anthony A. Kattine, M.D.
NEPHROTOXIC POTENTIAL OF BENCE JONES PROTEINS — SOLOMON ET AL.

NEPHROTOXIC POTENTIAL OF BENCE JONES PROTEINS

Alan Solomon, M.D., Deborah T. Weiss, B.S., and Anthony A. Kattine, M.D.

Mouse  Human

Mouse  Human

casts

Light chain crystals

Tubular basement membrane deposits

Congo red positive deposits
AL-amyloidosis and light-chain deposition disease light chains induce divergent phenotypic transformations of human mesangial cells
Both AL-LC & LCDD-LC bind the same receptor
# MGRS vs MGUS

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>MGRS</th>
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</thead>
<tbody>
<tr>
<td>Serum M-spike</td>
<td>&lt; 3 g/dl</td>
<td>&lt; 3 g/dl</td>
</tr>
<tr>
<td>Clonal BM Plasma Cells</td>
<td>&lt; 10%</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>C_AB</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Renal Disease (not cast nephropathy)</td>
<td>Not attributable to the monoclonal gammopathy</td>
<td>Attributable to the monoclonal gammopathy</td>
</tr>
<tr>
<td>Renal Diseases associated with MGRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organized</th>
<th>Crystals</th>
<th>Fibrillar</th>
<th>Microtubular</th>
<th>Nonorganized (granular)</th>
<th>MIDD (Randall type)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myeloma cast nephropathy</td>
<td>Light chain amyloidosis</td>
<td>Type I and type II cryoglobulinemic glomerulonephritis</td>
<td>LCDD</td>
<td>Proliferative GN with monoclonal Ig deposits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Light chain proximal tubulopathy (with or without Fanconi syndrome)</td>
<td>Nonamyloid</td>
<td>Immunotactoid GN</td>
<td>LHCDD</td>
<td>Waldenström</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crystal-storing histiocytosis</td>
<td>Fibrillary GN*</td>
<td>GOMMID</td>
<td>HCDD</td>
<td>Macroglobulinemia</td>
<td></td>
</tr>
</tbody>
</table>
## Kidney Diseases associated with Dysproteinemia

<table>
<thead>
<tr>
<th>Monoclonal only</th>
<th>Monoclonal/polyclonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cast nephropathy*</td>
<td>• Fibrillary glomerulonephritis</td>
</tr>
<tr>
<td>• Light chain Fanconi syndrome</td>
<td>• Immunotactoid glomerulonephritis</td>
</tr>
<tr>
<td>• AL amyloidosis</td>
<td>• Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>• MIDD</td>
<td>• C3 glomerulonephritis</td>
</tr>
<tr>
<td>• Cryoglobulinemic glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>• Waldenstrom macroglobulinemic glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>• Proliferative glomerulonephritis with monoclonal IgG deposits</td>
<td></td>
</tr>
</tbody>
</table>

* not MGRS

Markowitz GS. Adv Anat Path 2004
Immunotactoid glomerulonephritis
Immunotactoid glomerulonephritis

• Definition
  • Cryoglobulin (Rheumatoid factor) negative

• Histologic pattern
  • Membranoproliferative - > 50%
  • Membranous pattern
  • Endocapillary proliferative glomerulonephritis
  • Crescents are occasionally seen

• Immunofluorescence
  • IgG – 88%

• Electron
  • Mean fibril diameter – 31 (17 – 52) nm
  • Microtubules (hollow center)
<table>
<thead>
<tr>
<th></th>
<th>ITN</th>
<th>FGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibril size</td>
<td>10 – 52 nm</td>
<td>12 – 23 nm</td>
</tr>
<tr>
<td>Fibril orientation</td>
<td>parallel</td>
<td>random</td>
</tr>
<tr>
<td>Fibril center</td>
<td>hollow</td>
<td>solid</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>63 – 86%</td>
<td>15 - 17%</td>
</tr>
<tr>
<td>Hypocomplementemia</td>
<td>33 - 46%</td>
<td>2 - 9%</td>
</tr>
<tr>
<td>Proteinuria (g/d)</td>
<td>6.0 - 11.1</td>
<td>4.5 – 5.6</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>CLL</td>
<td>19 – 50%</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphoproliferative</td>
<td>6%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Membranoproliferative Glomerulonephritis

A. Idiopathic MPGN
- Type I
- Type II
- Type III

B. Secondary MPGN
(i) With immune deposits
- Infections
- Autoimmune diseases
- Dysproteinemias

(ii) Without immune deposits
- Chronic liver disease
- Thrombotic microangiopathies
- Diabetic nephropathy

MPGN
Dense deposit disease
Mixed features of type I MPGN and membranous GN

Cryoglobulinaemia (type II and III) HBV, HCV, endocarditis, visceral abscesses,
infected ventriculo-atrial shunts, malaria, schistosomiasis, mycoplasma, EBV, HIV
SLE, rheumatoid arthritis, Sjögren’s syndrome
Light or heavy chain deposition disease, cryoglobulinaemia type I or II,
Waldenstrom’s macroglobulinaemia, immunotactoid and fibrillary glomerulopathy

Cirrhosis, alpha-1-antitrypsin deficiency
HUS/TTP, anti-phospholipid antibody syndrome, radiation nephritis,
sickle cell anaemia, transplant glomerulopathy
Monoclonal Gammopathy: Significance and Possible Causality in Renal Disease

Paisit Paueksakon, MD, Monica P. Revelo, MD, PhD, Robert G. Horn, MD, Scott Shappell, MD, PhD, and Agnes B. Fogo, MD

Table 3. Patients With Disease Not Related to MGUS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases (%)</th>
<th>+SPEP</th>
<th>+UPEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>10 (18.1)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Focal segmental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulosclerosis</td>
<td>10 (18.1)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Arterionephrosclerosis</td>
<td>7 (12.7)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Membranous GN</td>
<td>5 (9.0)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>4 (7.3)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Membrano proliferative GN</td>
<td>3 (5.4)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Focal proliferative GN</td>
<td>2 (3.6)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pauci-immune GN</td>
<td>2 (3.6)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic immune complex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GN</td>
<td>2 (3.6)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>1 (1.8)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anti-GBM antibody-mediated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GN</td>
<td>1 (1.8)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chronic interstitial nephritis</td>
<td>1 (1.8)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nonspecific changes</td>
<td>7 (12.7)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>55 (100)</td>
<td>45</td>
<td>25</td>
</tr>
</tbody>
</table>
Membranoproliferative Glomerulonephritis

- 126 patients with MPGN I and III
  - Excluded
    - Not evaluated for hepatitis B or C – 20
    - Hepatitis B – 12
    - Hepatitis C – 13
    - Hepatitis B & C – 2
    - No monoclonal studies - 13
Membranoproliferative Glomerulonephritis Secondary to Monoclonal Gammopathy

Sanjeev Sethi,* Ladan Zand,† Nelson Leung,† Richard J.H. Smith,‡ Dragan Jevremonic,* Sandra S. Herrmann,† and Fernando C. Fervenza†

- 68 hepatitis negative patients
  - 24 monoclonal and 4 biclonal gammopathy
    - SPEP + in 25/28
    - UPEP + in 8/26
      - IgMκ - 10
      - IgGκ - 9
      - IgGλ - 4
      - λ - 1
  - Bone marrow Biopsy
    - MGUS – 16
      - CLL - 1
      - MM - 2
    - CLL – 2
    - Waldenström – 1
    - B-cell lymphoma – 3
    - Multiple myeloma – 6
Diagnosis of MGRS

By definition, MGRS requires a kidney biopsy that demonstrates the effect of the monoclonal gammopathy on the kidney.
Heavy chain and light chain restriction
Rates of MGUS >> Glomerular Disease

Kyle et al. NEJM 2006
Recurrent Goodpasture’s Disease Secondary to a Monoclonal IgA1-κ Antibody Autoreactive With the α1/α2 Chains of Type IV Collagen

Dorin-Bogdan Borza, PhD, Marcio F. Chedid, MD, Selene Colon, BS, Donna J. Lager, MD, Nelson Leung, MD, and Fernando C. Fervenza, MD, PhD

- 57 yo male with recurrent pulmonary hemorrhage and renal failure
- 100% crescents
- Anti-GBM test was negative
- IgAκ deposits were noted on kidney biopsy
- Monoclonal IgAκ was found in the serum
- Bone marrow biopsy – 5% - 10% plasma cells
- Kidney transplant was performed for ESRD
- Disease recurred 1 year later
C3 Glomerulonephritis

Glomerulonephritis With Isolated C3 Deposits and Monoclonal Gammopathy: A Fortuitous Association?


C3 Glomerulonephritis Associated With Monoclonal Gammopathy: A Case Series

Monoclonal protein acting like a C3 nephritic factor
IKMG Diagnostic Scheme

Kidney biopsy

Ig or light chain restriction on immunofluorescence

+ -

Serum and urine monoclonal studies (protein electrophoresis and immunofixation, sFLC)

Bone marrow biopsy

* Lymph node biopsy

*If bone marrow is negative and high suspicion for lymphoma

C3 predominant deposits

- No further hematologic work up

+ -

Monoclonal gammopathy

+ -

C3 nef and Anti-H autoantibodies

Nasr et al. Kidney Int (In submission)
<table>
<thead>
<tr>
<th>Test</th>
<th>Lower Limit of Detection</th>
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<tbody>
<tr>
<td>SPEP</td>
<td>500 mg/L</td>
</tr>
<tr>
<td>Immunofixation</td>
<td>150 mg/L</td>
</tr>
<tr>
<td>sFLC</td>
<td>0.5 mg/L</td>
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</table>
Sensitivity of current laboratory tests in MGRS related proliferative glomerulonephritis

- Serum and urine PEP + IFN – 18%
- sFLC – 18%
- S/U PEP + IFN + sFLC – 27%
- Clonal cell detected
  - + monoclonal gammopathy > 90%
  - - monoclonal gammopathy – 0%
MGRS

1. MGRS associated kidney diseases
2. The natural history of MGRS kidney diseases
3. How is MGRS diagnosed?
4. How is MGRS treated?
Questions

1. Does this patient have multiple myeloma?

2. Should this patient receive treatment?
   a) What type of treatment should he receive?
   b) Is multiple myeloma necessary for initiation of treatment?
   c) Can myeloma therapy be used if multiple myeloma is not present?

3. Will there be severe consequences if no treatment is offered?
Case #3
35 yo previously healthy female

- 8/03: Hypertension and microscopic hematuria. Scr – 0.8 mg/dl (71 μmol/L), 10 g/d proteinuria
- 9/03: Dx with LHCDD – Cyclophosphamide and prednisone
- 10/03: Bone marrow biopsy – inadequate sample
- 11/03: Thalidomide and dexamethasone were added but d/c due to increase edema
- 1/04: Scr =1.4 mg/dl (124 μmol/L), Proteinuria = 8.8 g/d
Disease course

- Acute cholecystitis
- Rituximab x 2
- MMF
- CyP
- Tacrolimus and dexamethasone

Graph showing changes in proteinuria (g/d) and Scr (mg/dl) over time.
Case #3 Cont

- 5/07  CMV colitis, Scr peaked at 5.0 mg/dl (442 μmol/L)
  - Bowel Resection
  - DVT
- 6/08  ESRD on hemodialysis
- 8/11  Kidney transplantation
  - Monoclonal IgAλ detect pretransplant
- 12/11 Scr -1.4 mg/dl (124 μmol/L)
  - Proteinuria 1.7 g/d
  - Monoclonal IgAλ on SPEP and UPEP
  - FLC: κ = 12.3 mg/dl, λ = 8.65 mg/dl, ratio 1.43
  - Kidney biopsy, IgAλ deposits
  - Bone marrow biopsy 30% λ light chain restricted plasma cells
- 1/12  Scr - 3.3 mg/dl
Old Treatment Paradigms for Nephrologists

Renal pathology → Treatment

Steroids → Mycophenolate → CNI → Cyclophosphamide → RTX
AL amyloidosis
AL and Multiple Myeloma

- In AL, only 15% meet criteria for multiple myeloma
  - 40% - > 10% bone marrow PC
  - 7% - > 3 g/dL of M-protein
  - 8.2% - lytic lesions
  - 3% had SMM
A TRIAL OF THREE REGIMENS FOR PRIMARY AMYLOIDOSIS: COLCHICINE ALONE, MELPHALAN AND PREDNISONE, AND MELPHALAN, PREDNISONE, AND COLCHICINE

Robert A. Kyle, M.D., Morie A. Gertz, M.D., Philip R. Greipp, M.D., Thomas E. Witzig, M.D., John A. Lust, M.D., Ph.D., Martha Q. Lacy, M.D., and Terry M. Therneau, Ph.D.

- Low response rate
  - Hematologic response rates of 20-30%
- Slow response time
  - 30% required more than 1 year to show response
- Not effective for cardiac AL
  - Median survival 5 -6 months
- Long term myelotoxicity
  - Risk of MDS and leukemia

Kyle et al. NEJM 1997
Overall Survival of AL Patients Treated with Melphalan Prednisone, ASCT and Melphalan Dexamethasone

Kyle et al. NEJM 1997, Gertz et al. Leukemia & Lymphoma 2010
Treatment should target the pathologic clone

- Clones that produce monoclonal gammopathy
  - B-cell
  - Plasma cell
  - B-cell with plasmacytic differentiation
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
Proposed Treatment Scheme

Glomerulonephritis with immunoglobulin deposits

Monoclonal deposits

Clone identified

Low Risk

CD20+
Rituximab

CD20-
CyBorD

High Risk

CD20+
R-CyBorD

CD20-
CyBorD

No clone

Low Risk

CyP x 3 months

No response
Rituximab

Response
Continue CyP

High Risk

CyBorD

Polyclonal deposits

As per Nephrology

Low risk = serum creatinine < 1.5 mg/dL proteinuria < 2 g/d
• Non – nephrotoxic
• Renal dosing only for cyclophosphamide
• Manageable toxicity
Reduction in Proteinuria and Renal Function in AL patients

Reduction in proteinuria and Overall Survival in AL amyloidosis
Patient Survival after Kidney Transplantation in AL Amyloidosis Patients Who Achieved Hematologic Complete Response

![Graph showing patient survival over follow-up time](image)

- **KTX followed by ASCT (n=8)**
- **ASCT followed by KTX (n=6)**
- **KTX only (n=5)**

Log rank 0.12, p=0.94
Improvement in Renal Function in Patients with LCDD after Autologous SCT

Lorenz et al. Nephrol Dial Transplant 2008
Chronic lymphocytic leukemia associated with immunotactoid glomerulopathy: a case report of successful treatment with high-dose methylprednisolone in combination with rituximab followed by alemtuzumab

Januario
Noel Weic

Kidney Function

S. Barajas-Gi

Proteinuria

Creatinine (mg/dl)

Total protein, urine (mg/day)

Months after initiation of treatment

CD19 FITC

CD5PE

84.6%

0.06%

0.07%

2.03%
LETTER TO THE EDITOR

Renal Fanconi syndrome as a cause of chronic kidney disease in patients with monoclonal gammopathy of undetermined significance: partially reversed renal function by high-dose dexamethasone with bortezomib

Yuki Nishida, Kan-ichi Iwama, Masayuki Yamakura, Masami Takeuchi & Kosei Matsue
Treatment goals of MGRS

• Preservation of renal function
• Restore eligibility for kidney transplantation
• Improve life expectancy (AL amyloidosis)
• Minimize adverse effects of chemotherapy
Summary

• MGRS is a clonal B-cell condition that does not qualify for a malignancy but results in kidney disease

• Treatment with cytotoxic agents is required for MGRS

• Diagnosis is based on demonstration of the effect of the monoclonal gammopathy on the kidney

• Treatment should target the clone responsible for monoclonal gammopathy
Questions

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida