Clinical Work Up and Treatment of Monoclonal Gammopathy of Renal Significance

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Nephrology and Hypertension/ Hematology
Mayo Clinic Rochester
Conflict of Interest

Conflict of interest statement: Senior author's promotion and first author's job depend on this study.
Monoclonal Gammopathy of Undetermined Significance (MGUS)

- First used in 1974 in the description of 241 patients

- Other names used prior to MGUS
  - Benign
  - Essential
  - Idiopathic
  - Asymptomatic
Monoclonal Gammopathy of Renal Significance (MGRS)

• What is MGRS
• The natural history of MGRS
• How to diagnose MGRS
• Treatment principles of MGRS
Case #1

• 51 yo previously healthy Royal Canadian Mounted Police
  • 4 years prior developed
    • Arthralgias
    • Fatigue
    • Vasculitic rash – biopsy suggests cryoglobulinemia
    • Cryoglobulins were negative
  • Presented in February 2 years earlier
    • Shortness of breathe
    • Acute renal failure
      • Creatinine = 4.1 mg/dL
    • Renal biopsy was obtained
Case cont.

- Diagnosis of “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 years 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 IgGκ
  - M-spike – 0.4 g/dL
  - BM showed 1% plasma cells
  - Bone survey showed no lytic lesions
Questions

• What did this patient have?
• Does he have multiple myeloma?
• Should he receive myeloma therapy?
• If not, what are the consequences?
Crystalline IgG\textsubscript{\kappa} thrombi with periodicity
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

- Often associated with multiple myeloma but some are not
- Cryoglobulins are typically negative
- Thrombosis most often occur in the periphery
- Central thrombosis is almost always reported in fulminant end stage myeloma patients
## Diagnostic Criteria of Plasma Cell Dyscrasias

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<th>MGUS</th>
<th>SMM</th>
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<td>Lytic lesions (B)</td>
<td>absent</td>
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</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
Prognostication models for progression of smoldering multiple myeloma

Dispenzieri et al. Blood 2013
Further Evaluation

• Ca – 9.7 mg/dL
• Cryoglobulins were negative
• Immunofixation – small monoclonal IgGκ
  • M-spike – 0.4 g/dL
  • BM showed 1% plasma cells
  • Bone survey showed no lytic lesions
• Intermediate and high risk MGUS. If a patient with apparent MGUS has a serum monoclonal protein 415 g/l, IgA or IgM protein type, or an abnormal FLC ratio, a BM aspirate and biopsy should be carried out at baseline to rule out underlying PC malignancy…Treatment is not indicated unless it is part of a clinical trial. Patients must contact their physician if there is any change in their clinical condition.
Questions

• What did this patient have?
• Does he have multiple myeloma? NO
• Should he receive myeloma therapy?
• If not, what are the consequences?
Questions

• What did this patient have?
• Does he have multiple myeloma? **NO**
• Should he receive myeloma therapy? **NO**?
• If not, what are the consequences?
Probability of Progression to Multiple Myeloma or AL Amyloidosis

Kyle et al. NEJM 2007
AL and Renal Outcome

- In AL, only 15% meet criteria for multiple myeloma
  - 40% - > 10% bone marrow plasma cells
  - 7% - > 3 g/dL of M-protein
  - 8.2% - lytic lesions
  - 3% had SMM

- 1993 – 1997
- Treatment
  - Melphalan prednisone
  - High dose dexamethasone
- Response rates ~20%

Kyle & Gertz. Sem in Hematol. 1995
Gertz et al. NDT 2009
Renal Survival of MIDD with or without myeloma

Lin et al. JASN 2001
Renal Outcomes of PGNMID

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Peripheral edema (n [%])</td>
<td>23 (62.2)</td>
</tr>
<tr>
<td>24-h urine protein (g/d; mean [range])</td>
<td>5.70 (0.36 to 17.00)</td>
</tr>
<tr>
<td>Proteinuria &lt;1 g/24 h (n [%])</td>
<td>1/35 (2.9)</td>
</tr>
<tr>
<td>Proteinuria 1–3g/24 h (n [%])</td>
<td>10/35 (28.6)</td>
</tr>
<tr>
<td>Proteinuria &gt;3g/24 h (n [%])</td>
<td>24/35 (68.6)</td>
</tr>
<tr>
<td>Full nephrotic syndrome (n [%])</td>
<td>17/35 (48.6)</td>
</tr>
<tr>
<td>Serum albumin (g/d; mean [range])</td>
<td>3.1 (1.1 to 4.9)</td>
</tr>
<tr>
<td>Hematuria (n [%])</td>
<td>27/35 (77.1)</td>
</tr>
<tr>
<td>Serum creatinine at biopsy (mg/dl; mean [range])</td>
<td>2.77 (0.70 to 17.00)</td>
</tr>
<tr>
<td>Renal insufficiency at presentation (n [%])</td>
<td>25 (67.6)</td>
</tr>
</tbody>
</table>

Evidence of dysproteinemia (n [%])a
- Serum paraprotein only: 4
- Serum and urine paraprotein: 7
- Multiple myeloma: 1
- AL amyloid: 1

<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>
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<tr>
<td>cyclophosphamide</td>
<td>3</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>2</td>
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<tr>
<td>mycophenolate mofetil</td>
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<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>
</tbody>
</table>

Outcomea

| CR                                           | 4 (12.5)   |
| PR                                           | 8 (25.0)   |
| PRD                                          | 12 (37.5)  |
| Persistent hematuria (with normal creatinine and no proteinuria) | 1 (3.1)  |
| ESRD                                         | 7 (21.9)   |
| Death                                        | 5 (15.6)   |
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
Recurrent membranoproliferative glomerulonephritis after kidney transplantation

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

Proportion of patients with recurrent MPGN

Month of recurrence

Proportion of patients with rMPGN

Months post-transplant

Proportion of patients with rMPGN

Serum monoclonal proteins and rMPGN

P = 0.08

P = 0.02

Kidney Int 2010; 77: 721–8
Recurrence and Graft Survival with and without MG in Fibrillary Glomerulonephritis

![Graph showing recurrence and graft survival with and without MG in fibrillary glomerulonephritis.](image-url)

- Proportion Recurred: 0.10
- Allograft survival: 0.24

Czarnecki et al. Kidney Int 2009
# Proliferative Glomerulonephritis with Monoclonal IgG Deposits Recurs in the Allograft


<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Kidney source</td>
<td>Living-unrelated donor</td>
<td>Deceased donor</td>
<td>Living-related 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>
</tr>
<tr>
<td>Percent PRA</td>
<td>1% for class I</td>
<td>0% for class I</td>
<td>0% for class I</td>
</tr>
<tr>
<td>Percent PRA</td>
<td>13% for class II</td>
<td>0% for class II</td>
<td>0% for class II</td>
</tr>
<tr>
<td>Maintenance immunosuppressive regimen</td>
<td>FK506/PRED/MMF</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>
</tr>
<tr>
<td>Baseline serum creatinine (mg/dl)</td>
<td>1.9</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Parameters at the time of first biopsy showing recurrence</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>
</tr>
<tr>
<td>24-hour urine protein</td>
<td>0.790</td>
<td>7.4</td>
<td>5.8</td>
</tr>
<tr>
<td>serum albumin</td>
<td>3.5</td>
<td>2.0</td>
<td>3</td>
</tr>
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Questions

- What did this patient have?
- Does he have multiple myeloma? **NO**
- Should he receive myeloma treatment? **NO**?
- If not, what are the consequences? **ESRD/Recurrence after kidney transplant**
Questions

• What did this patient have?
• Does he have multiple myeloma? NO
• Should he receive myeloma treatment? Yes
• If not, what are the consequences? ESRD/Recurrence after kidney transplant
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Kyle et al. Leukemia 2010
Talamo et al. Clin Lymphoma, Myeloma & Leukemia. 2010
International Kidney and Monoclonal Gammopathy Research Group

blood
2012 120: 4292-4295
Prepublished online October 9, 2012;
doi:10.1182/blood-2012-07-445304

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
## MGRS vs MGUS

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<thead>
<tr>
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<th>MGUS</th>
<th>MGRS</th>
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<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>
</tbody>
</table>
Dangerous small B-cell clones

Giampaolo Merlini and Marvin J. Stone
# Tumor burden in MGRS

## Low tumor burden
- **Glomerular**
  - MIDD
  - AL/AH/ALH amyloidosis
  - MPGN
  - PGNMID
  - Immunotactoid GN
  - Fibrillary GN with MG
  - Cryoglobulinemia Type I
  - C3 glomerulonephropathy with MG
- **Tubular**
  - Fanconi syndrome
  - Proximal tubulopathy
  - Crystal storage histiocytosis

## High tumor burden
- **Cast nephropathy**
- **Lymphomatous infiltration**
- **Hyperviscosity**

---

Bridoux et al. Kidney Int 2015
• Scr > 2 mg/dl or eGFR < 40 ml/min/1.73 m²

• Only renal failure caused by light-chain cast nephropathy
  • presence of high involved FLC levels, typically >1500 mg/L)

• AL amyloidosis, monoclonal immunoglobulin deposition disease, light chain Fanconi syndrome, monoclonal gammopathy associated membranoproliferative glomerulonephritis) can occur in multiple myeloma, *this association is not characteristic of multiple myeloma*
Classification of MGRS renal lesions by deposits

MGRS-associated renal lesions

- Organized deposits or inclusions
  - Fibrils
    - Ig-related amyloidosis (AL, AHL, AH)
    - Fibrillary GN
  - Microtubules
    - Immunoactoid GN/GOMMID
  - Crystals or inclusions
    - Light chain proximal tubulopathy (with or without Fanconi syndrome)
    - Crystal-storing histiocytosis

- Non-organized deposits/inclusions
  - Monoclonal immunoglobulin deposition disease (LCDD, LHCDD, HCDD)
  - Proliferative GN with monoclonal Ig deposits (PGNMID)
  - C3 glomerulopathy associated with monoclonal gammopathy
Spectrum of Monoclonal Gammopathy

- MGUS
- Monoclonal B cell lymphocytosis
- Monoclonal plasmacytosis
- Lymphoma/ Chronic Lymphocytic Leukemia
- Lymphoma
- Multiple Myeloma/ Plasma cell leukemia
- Lymphoplasmacytic/ Waldenström’s
- PLASMACYTOMA
- Cancer
### Spectrum of Hematologic Diseases

<table>
<thead>
<tr>
<th>Renal lesion</th>
<th>Hematologic diseases</th>
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<tbody>
<tr>
<td>Cast nephropathy</td>
<td>MM, Waldenström, CLL</td>
</tr>
<tr>
<td>Alg amyloidosis</td>
<td>MGRS, MM, Waldenstrom, CLL</td>
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<td>MIDD</td>
<td>MM, MGRS, CLL, Waldenström</td>
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<tr>
<td>MPGN</td>
<td>MGRS, MM, B-cell, CLL, Waldenström</td>
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<td>Immunotactoid</td>
<td>CLL, MM, Waldenström</td>
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Kidney Diseases Associated with Monoclonal Gammopathy

Monoclonal gammopathy

- Light chain
  - Cast nephropathy
  - Fanconi’s syndrome

- Heavy chain
  - Amyloidosis
  - MIDD
  - GMA (POEMS)
  - MPGN
  - Immunotactoid GN
  - PGNMID (Nasr type)
  - Cryoglobulinemia
  - Waldenstrom macroglobulinemic GN

Immunoglobulin
Diagnostic Criterion for MGRS

• Demonstrate the involvement of a monoclonal immunoglobulin or its component in the pathophysiology of the kidney disease.
Heavy chain and light chain restriction

IgA

kappa

IgA1  IgA2

IgG1  IgG2

IgG3  IgG4

Mayo Clinic
Immunogold
Proteomics detection of the Ig variable region

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<th>Bio View: Identified Proteins (402/406)</th>
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<th>Sample 2</th>
<th>Sample 3</th>
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<tr>
<td>1</td>
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<td>Serum amyloid P-component</td>
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<td>6</td>
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<td>Ig lambda chain C regions</td>
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<td>3</td>
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<td>Apolipoprotein E precursor</td>
<td>7</td>
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<td>Hemoglobin subunit beta</td>
<td>33</td>
<td>63</td>
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<td>Ig lambda variable Region VI Locus 16a</td>
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<td>Ig Lambda Constant Region 2 J00253</td>
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<td>Apolipoprotein E</td>
<td>6</td>
<td>4</td>
<td>10</td>
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<tr>
<td>5</td>
<td></td>
<td>Hemoglobin subunit beta</td>
<td>30</td>
<td>54</td>
<td>43</td>
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</tbody>
</table>

Variable region
• 57 yo male with recurrent pulmonary hemorrhage and renal failure
• 100% crescents
• Anti-GBM test was negative
• IgA_κ deposits were noted on kidney biopsy
• Monoclonal IgA_κ was found in the serum
• Bone marrow biopsy – 5% - 10% plasma cells
• Kidney transplant was performed for ESRD
• Disease recurred 1 year later
Case #3

- 52 yo male with 13 year history of membranous nephropathy
- Undergoes deceased donor kidney transplantation
- Delay graft functioning until Day 13
  - Cr 2.82 mg/dl
  - Proteinuria 1.85 g/d
- An allograft biopsy was performed
Renal biopsy
Recurrent Membranous Nephropathy in an Allograft Caused by IgG3κ Targeting the PLA2 Receptor

Hanna Debiec,*†† Melanie Hanoy,§ Arnaud Francois,‖ Dominique Guerrot,§ Sophie Ferlicot,** Catherine Johanet,†† Pierre Aucouturier,‡‡ Michel Godin,§‖ and Pierre Ronco*††

[Caption: Images showing PLA2R expression in renal tissue]

Rates of MGUS >> Glomerular Disease

Kyle et al. NEJM 2006
C3 Glomerulonephritis

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

Frank Bridoux, Estelle Desport, Véronique Frémeaux-Bacchi, Christine Fen Chong, Jean-Marc Gombert, Corinne Lacombe, Nathalie Quellard, and Guy Touchard

C3 Glomerulonephritis Associated With Monoclonal Gammopathy: A Case Series

Ladan Zand, MD, Andrea Kattah, MD, Fernando C. Fervenza, MD, PhD, Richard J.H. Smith, MD, Samih H. Nasr, MD, Yuzhou Zhang, PhD, Julie A. Vrana, PhD, Nelson Leung, MD, Lynn D. Cornell, MD, and Sanjeev Sethi, MD, PhD
Monoclonal Ig acting as a C3 nephritic factor (C3nef) or Factor H autoantibody
Diagnosis of monoclonal gammopathy of renal significance

Frank Bridoux¹, Nelson Leung², Colin A. Hutchison³, Guy Touchard¹, Sanjeev Sethi⁵, Jean-Paul Fermand⁶, Maria M. Picken⁷, Guillermo A. Herrera⁸, Efstathios Kastritis⁹, Giampaolo Merlini¹⁰, Murielle Roussel¹¹, Fernando C. Fervenza², Angela Dispensieri³, Robert A. Kyle³, Samih H. Nasr⁵ on behalf of the International Kidney and Monoclonal Gammopathy Research Group

Kidney biopsy

Ig or light chain restriction on immunofluorescence

+ -

C3 predominant deposits

No further hematologic workup

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

Bone marrow aspirate and biopsy

Lymph node biopsy

*If bone marrow is negative and high suspicion for lymphoma

C3 nef and anti-H autoantibodies

Monoclonal gammopathy

MAYO CLINIC

Bridoux et al. Kidney Int 2015
Current Treatment Paradigm in Nephrology

Pathophysiology → Treatment
# Ultrastructure Classification of MPGN

<table>
<thead>
<tr>
<th>Membranoproliferative glomerulonephritis</th>
<th>Associated with systemic and infectious disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>Idiopathic</strong></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td></td>
</tr>
<tr>
<td>Type II (dense deposit disease)</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>Viral: Hepatitis B and C, human immunodeficiency virus</td>
</tr>
<tr>
<td></td>
<td>Bacterial: shunt nephritis, visceral abscesses, infective endocarditis</td>
</tr>
<tr>
<td></td>
<td>Protozoal: quartan malaria, schistosomiasis, leprosy</td>
</tr>
<tr>
<td></td>
<td>Other: mycoplasma, mycobacteria</td>
</tr>
<tr>
<td></td>
<td>Mixed cryoglobulinemia</td>
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<td>Systemic lupus erythematosus</td>
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<td>Scleroderma</td>
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<td>Sjögren's syndrome</td>
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<td>Hereditary deficiencies of complement components</td>
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<td>Hypocomplementemic urticarial vasculitis</td>
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<td>Leukemias and lymphomas</td>
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<td>Carcinomas</td>
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<td>Light-chain disease and plasma cell dyscrasias</td>
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<td>Chronic hepatitis</td>
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<td>Cirrhosis</td>
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<td>Partial lipodystrophy</td>
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<td>α1-Antitrypsin deficiency</td>
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<td>Cystic fibrosis</td>
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<td>Drugs (e.g., heroin, α-interferon)</td>
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<td>Sarcoidosis</td>
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<td>Sickle cell disease</td>
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<td>Hemolytic uremic syndrome</td>
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<td>Transplant glomerulopathy</td>
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<td><strong>Systemic immune complex diseases</strong></td>
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<td><strong>Neoplasms</strong></td>
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<td><strong>Chronic liver disease</strong></td>
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<td><strong>Miscellaneous</strong></td>
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</table>
Management of membranoproliferative glomerulonephritis: Evidence-based recommendations

- > 3 g/d proteinuria, interstitial disease or impaired kidney function
- Children – high dose steroids
- Adults – dipyridamole or aspirin

Levin. Kidney Int 1999
Membranoproliferative Glomerulonephritis — A New Look at an Old Entity

Sanjeev Sethi, M.D., Ph.D., and Fernando C. Fervenza, M.D., Ph.D.
Immunofixation Based Classification

MPGN (novel classification)
Based on IF

Ig and complements

Monoclonal

Proceed with
Clinical evaluation and testing for monoclonal proteins: serum free light chains and immunofixation +/- SPEP and UPEP

Polyclonal

Proceed with
Clinical evaluation and testing for infection emphasis on hepatitis B and C

C3 dominant

C3 GN

Proceed with
Testing if available for complement dysregulation, consider referring to a C3 glomerulonephritis center

DDD

Null complements and null Ig

TMA

If none of the above – idiopathic MPGN

Masani et al. CJASN 2014
Time line of Molecular Classification in Breast Cancer

- **ER**: Dextran coated charcoal beads to quantify ER
- **1970**: Loss of Heterozygosity (LOH) and Comparative Genomic Hybridization (CGH) (losses, gains and amplifications of genomic DNA sequences)
- **1990**: Immunohistochemistry for ER on tissue sections
- **2000**: New molecular subtypes
  - Claudin-low
  - Molecular apocrine
  - Interferon-related
- **2010**: Massively Parallel Sequencing
  - TCGA (>500 tumours)
  - ICGC (>100 tumours)
  - Data analysis across multiple platforms (DNA copy number arrays, DNA methylation, exome sequencing, RNA arrays and sequencing, proteomics)
- **2014**: Integrated gene expression and DNA copy number analysis
  - METABRIC
  - (2,000 breast cancers)
  - 10 integrative clusters

- **1970**: Gene expression based prognostic signatures
  - OncotypeDX®
  - MammaPrint®
  - PAM50
- **2010**: Targeted gene sequencing cancer gene panels

Vuong et al. Virchows Arch 2014
Diffuse Large B-cell Lymphoma

R-CHOP
Response to Therapies Based on Subtype

DLBCL

- R-CHOP
- Bortezomib
- EPOCH
- Ibrutinib*

GCB
- Histone modification
  - EZH2 mutations
  - MLL2 mutations
  - CREBBP mutations
  - EP300 mutations
- Blocks to terminal differentiation
  - BCL6 expression, EZH2 mutations
- Cell cycle activation +/- blocks to apoptosis
  - MYC and BCL2 translocations (DHIT) and protein over-expression
- MTOR pathway activation
- Signaling cascades
  - PTEN del/loss (PI3K and AKT activation)

ABC
- BCR/NF-κB signaling
  - CD79A/B, CARD11, MYD88 mutations, TNFAIP3 (A20) deletions
- Histone modification
  - MLL2 mutations
  - CREBBP mutations
  - EP300 mutations
- Blocks to terminal differentiation
  - BCL6 translocations, PRDM1 loss/ mutations
- Cell cycle activation +/- blocks to apoptosis
  - MYC translocations, MYC and BCL2 protein over-expression
- MTOR pathway activation
- Signaling cascades
  - PI3K and AKT activation
- Cytokine signaling/JAK-STAT pathway activation

Wilson et al. ASH abstract 623
Sehn et al. Blood 2015
Dunlevey et al. Oncology 2014
Current Treatment Strategy

Steroids  Mycophenolate Mofetil  Rituximab
Case #4

• 8/2003
  • 35 yo female presents with edema and hypertension
    • Scr was 0.8 mg/dl (70 μmol/L)
    • Proteinuria 10 g/d
    • SPEP/UPEP/IFN – negative
    • Renal biopsy was performed 9/2003
    • Initial diagnosis – light heavy chain deposition disease
    • Bone marrow – non diagnostic
Proliferative glomerulonephritis with monoclonal IgA1λ
Disease course of a patient with MPGN with IgAλ

- 9/1/2003: BM Bx (-)
- 10/1/2003: Acalculous cholecystitis
- 11/1/2003: Rituximab x 2
- 12/1/2003: MMF
- 1/1/2004: CyP
- 2/1/2004: Tacrolimus, dexamethasone
- 3/1/2004: CyP
- 4/1/2004: Proteinuria (g/d)
- 5/1/2004: Scr (mg/dl)
Case #4

- 5/2007 CMV colitis, Scr peaked at 5.0 mg/dl (442 μmol/L)
  - Bowel resection
  - DVT
- 6/2008 ESRD on chronic dialysis
- 6/2011 Kidney transplantation
  - Monoclonal IgA detected pretransplant
- 12/2011 Scr 1.4 mg/dl (124 μmol/L)
  - Proteinuria 1.7 g/d
  - SPEP and UPEP – monoclonal IgA
  - Serum FLC : κ = 12.3 mg/L, λ = 8.65 mg/L, ratio = 1.43
  - Kidney biopsy – recurrent proliferative GN with IgA deposits
  - Bone marrow biopsy – 30% λ light chain restricted PC
- 1/2012 Scr 3.3 mg/dl (290 μmol/L)
Goal of evaluation is to link the kidney disease with the clone responsible for the Mlg
Efficacy of Rituximab against B-cell clones

B-cell CD20^+ | efficacy

- CLL/SLL
- Lymphoplasmacytic

Plasma cells
Clone Directed Therapy

• **B-cell**
  - (CD20⁺, κ or λ)

• **Lymphoplasmacytic (LPL)**
  - (sIgM⁺, CD19⁺, CD20⁺, CD22⁺, CD79⁺, CD138⁺, CD10⁻, MYD88 L265P)

• **CLL**
  - (CD5⁺, CD19⁺, CD20dim, CD23⁺, κ or λ)

Rituximab based therapy

RCD (rituximab/cyclophosphamide/dexamethasone)
Bendamustine Rituximab

FCR (fludarabine/cyclophosphamide/rituximab)
PCR (pentostatin/cyclophosphamide/rituximab)
Alemtuzumab
Chlorambucil – older patients
Plasma cell therapy

- **Plasma cell**
  - (CD38+, CD138+, κ or λ)

- Proteasome inhibitors
- IMiDs (immunomodulatory drugs)
- Alkylators
- Stem cell transplantation
Prednisone vs Dexamethasone

Complete response - rare
Median survival - 18 mo

Complete response – 33%
Median survival 5.1 year

Kyle et al. NEJM 1997
The Relationship between Hematologic and Renal Response

<table>
<thead>
<tr>
<th>Hematologic response</th>
<th>Renal response</th>
<th>Proteinuria reduction &gt;75%</th>
<th>Proteinuria reduction &gt;95%</th>
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</thead>
<tbody>
<tr>
<td>CR</td>
<td>72.4%</td>
<td>73.7%</td>
<td>52.6%</td>
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<tr>
<td>VGPR</td>
<td>55.1%</td>
<td>46.9%</td>
<td>16.3%</td>
</tr>
<tr>
<td>PR</td>
<td>25%</td>
<td>25%</td>
<td>0%</td>
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<tr>
<td>NR</td>
<td>25%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Reduction in Proteinuria and Renal Function in AL patients


Responders
Non-responders

Months After ASCT

% Proteinuria Change

0 3 6 9 12 18 24 36 48 60 72

Declined  Unchanged  Improved

Patients (%)
Renal Response and Overall Survival

Leung et al. Haematologica 2013
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
Patient Survival after Kidney Transplantation in AL Amyloidosis Patients Who Achieved Hematologic Complete Response
Case #5

• 2008
  • 46 year old male developed Guillain Barré syndrome after a viral illness
  • Motor and sensory neuropathy to above the knee
• 12/2010
  • patient suddenly felt poorly and went to the ED
  • Hypertensive
  • Renal failure with a creatinine of 4.3 mg/dl
  • Denied rash or arthralgia
Case #5

- **Renal biopsy**
  - A membranoproliferative glomerulonephritis with pseudothrombi.
  - IF showed IgM - 1-2+, C1q - 4+,
  - IgG, IgA, kappa and lambda were all negative.

- **Laboratory evaluation**
  - Cryoglobulin was positive
  - SPEP revealed an **IgG lambda** with a M-spike of 0.5 g/dl.
  - Urine studies showed > 7 g/d of proteinuria.
  - C3 and C4 were low
  - ANA, ANCA, Hep and HIV serologies were negative.

- **Bone marrow biopsy**
  - 5% plasma cells with a lambda predominance.

- **Diagnosis: Type II cryoglobulinemia**
Case #5

• Treatment
  • Cytoxan prednisone from 1/11 until 12/11
    • During this time, creatinine went down to 0.9 mg/dl
    • M-spike only reached as low as 0.4 mg/dl
    • Neuropathy symptoms improved
  • 7/13: hypertension worsened and creatinine was increasing
    • Rituximab (4 doses) starting in 10/13
    • Single dose repeated in Jan and Feb of 2014
      • Creatinine continued to climb to 2.7 mg/dl
      • Proteinuria 4.4 g/d
      • M-spike = 0.7 g/dl
      • Cryoglobulins are negative
      • C4 and C3 are low
      • Neuropathy improved with rituximab
Question

• Which test would be the most helpful in determining his treatment?

1. Bone marrow biopsy
2. Cryoglobulins
3. Free light chain assay
4. Kidney biopsy
5. Bone survey
Which monoclonal protein is involved?

Cryoglobulin

- IgM
  - LPL, B-cell
    - Rituximab
      - +
    - ???

- IgG
  - Plasma cell
  - Proteasome Inhibitor
  - IMiDs
Renal biopsy
Pronase retrieval Immunofixation

IgG

kappa
Treatment

- Modified CyBorD with reduced dose cyclophosphamide and bortezomib.
- If neuropathy worsens, would switch to lenalidomide based therapy.
Questions

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida
Which of the following classification provide the most pathophysiologic information about this lesion?

A. Ultrastructure based classification (i.e. Type I, II, III)
B. International Society of Nephrology/Renal Pathology Society Classification
C. Oxford Classification
D. Immunofluorescence based classification
E. Banff Classification 2013
Answer

D. Immunofluorescence based classification.

The immunofluorescence based classification for membranoproliferative glomerulonephritis provide the most information regarding the etiologic agent (i.e., immunoglobulins, complement or others such as thrombotic microangiopathy). The ultrastructure based classification is based on electron microscopy findings and does not provide etiologic data except for type II MPGN. ISN/RPS classification is for lupus nephritis. The Oxford classification is for IgA nephropathy and Banff classification is for renal allografts.
Which of the following MGRS associated kidney lesion is characterized by a lack of monoclonal immunoglobulin deposits in the kidney?

A. Heavy chain deposition disease
B. Immunotactoid glomerulopathy
C. AL (immunoglobulin light chain) amyloidosis
D. C3 glomerulonephritis with monoclonal C3 nephritic factor (C3nef)
E. Cryocrystalglobulinemic glomerulonephritis
Answer

D. C3 glomerulonephritis with monoclonal C3 nephritic factor (C3nef)

C3 glomerulonephritis is defined by predominate C3 deposits and little or no immunoglobulin deposits. The monoclonal protein in these patients acts to stabilize C3 convertase which perpetuate the complement cascade but is not deposited. All of the other lesions have monoclonal light chain, heavy chain or entire immunoglobulin deposits demonstrable in the kidney.
Which of the following is a characteristic of MGRS associated kidney diseases?

A. Progression to end stage renal disease is rare.
B. The diagnosis is made by standard electron microscopy.
C. Recurrence after kidney transplantation is common.
D. Rituximab is the most effective treatment for all MGRS associated kidney diseases.
E. Immunofluorescence studies are unhelpful for the diagnosis.
Answer

C. Recurrence after kidney transplantation is common especially if the monoclonal gammopathy is present.

While the rates differ depending on the disease, rates of greater than 80% have been reported for MGRS associated kidney diseases. One of the biggest determinant of recurrence is the presence of a monoclonal protein at the time of transplantation.