Case #3

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Clinical History

- 48 year-old nondiabetic Caucasian female
- Hepatitis C virus infection, diagnosed 8 years ago
- Liver biopsy one year before current presentation; Chronic hepatitis with minimal activity (Garde 1 of 4), Mild portal and periportal fibrosis (Stage 2 of 4)
- She was started on weekly 100 mg peginterferon α
- Viral load became undetectable, LFT were normal
Clinical History

• Three weeks before the kidney biopsy: lower extremity and facial swelling, fatigue, nausea, occasional vomiting and diarrhoea
• She developed skin lesions which were interpreted as cold erythema
• On presentation Her BP was 163/86 mm Hg
• No fever, BMI 24 (weight 147 lb, height 5’ 5’’)
• Medications: peginterferon α, furosemide, losartan, Percocet, aspirin, clonazepam
Laboratory Data

- Serum Cr 1.3 mg/dl (up from a baseline of 0.9 mg/dl)
- 9 g/24 hour proteinuria, microscopic hematuria (5-10 RBC/HPF)
- Serum albumin 1.7 g/L
- Serum C3: 40 mg/dl, C4: 4 mg/dl
- ANA negative
- Pancytopenia (WBC: 1900 to 2700/µL, Platelet: 59,000 to 100700/µL, Hgb 9.1 g/dL, HCT: 27)
- LFT normal
- SPAP, UPAP: no monoclonal spike
Imaging Studies (CT)

- Slightly enlarged inguinal and iliac lymph nodes
- Borderline enlargement of pulmonary hilar lymph nodes
- Scattered small calcified lung nodules on both sides along the bases.
- Liver, spleen: unremarkable
Renal Biopsy Findings
Kappa
Ig Heavy Chain Gene Rearrangement Study

Because of the IgG1 kappa monoclonal glomerular deposits and the kappa dominant staining in the focally dense interstitial mononuclear cell infiltrates with B cell clusters, Ig heavy chain gene rearrangement study was requested in the remnant of the paraffin block.

Result:

**Monoclonal**
There was excellent DNA amplification
Diagnosis

• Active diffuse intracapillary proliferative immunotactoid glomerulonephritis with large glomerular IgG1 kappa positive deposits, consistent with type I cryoglobulinemia-associated glomerulonephritis

• Likely infiltration of the renal parenchyma by B cell lymphoma
Follow-up

- Serum cryocrit was positive at 2% but rheumatoid factor was negative (<10).
- Serum and urine immunofixation were negative for monoclonal protein.
- A Bone marrow biopsy: slightly increased polyclonal plasma cells but no evidence of lymphoproliferative disease. Flow cytometry of the bone marrow did not indicate a monoclonal B cell population.
Follow-up

- Immediately, 500 mg/day Solumedrol was started followed by 100 mg/day prednisone, which was slowly tapered and stopped 6 months after the biopsy.
- Three weeks after the biopsy, the serum Cr. decreased to 0.85 mg/dl and urine P/Cr ratio was 3.2.
- Three months after the biopsy: Serum Cr.: 1.0 mg/dl, Urine P/Cr ratio: 0.2
- She has been in stable condition with no relapse at last follow-up (9 months). Her hepatitis viral load is undetectable.
Follow-up

• A PET scan (10 days after the biopsy):
  – Mediastinal lymph node up to 1.0 cm, inguinal and pelvic lymph nodes up to 1.0 cm, one 3.4 cm right external iliac lymph node

• CT scan three months later (at the time of remission of renal disease):
  – Unremarkable findings; no lymphadenopathy, the large external iliac lymph node was not detected.
Differential Diagnosis

1. Immunotactoid glomerulonephritis

- In fact, this case is an immunotactoid glomerulonephritis because the deposits have an organized substructure and contain immunoglobulin.

- In this patient the disease is most likely related to an (“occult”) B cell lymphoma and subsequent monoclonal cryoglobulinemia.

- Immunotactoid glomerulonephritis not related to cryoglobulinemia or lymphoma/multiclonal gammopathy is exceedingly rare (we probably just cannot detect the underlying disease).
Differential Diagnosis

2. Fibrillar glomerulonephritis

- **Pro:**
  - IgG kappa dominant deposits with fibrillar/microtubular substructure (diameter of 12.2 nm)
  - There is a weak association of FGN and hepatitis C virus infection
- **Contra:**
  - Deposits are not merely IgG kappa dominant but IgG1 kappa monoclonal
  - The 12.2 nm “fibrils on high magnification have a microtubular appearance
  - The fibrils/microtubules are localized to discrete deposits; they are not present throughout the glomerular extracellular matrix.
  - The fibrils/microtubules are not randomly arranged; the form paracrystalline structures with parallel arrangement
  - Large “glassy” glomerular capillary deposits and glomerular capillary “hyalin thrombi”
Differential Diagnosis

3. Cryoglobulinemic GN related to hepatitis C infection and type II cryoglobulinemia

• Pro:
  – Patient is hepatitis C virus positive
  – Large glassy glomerular capillary deposits and hyalin thrombi in the setting of proliferative glomerulonephritis

• Contra:
  – The glomerular deposits are monoclonal (IgG1 kappa). In Hepatitis C virus related cryoglobulininemic GN the deposits contain IgM and polyclonal IgG
  – Undetectable Hepatitis C viral load
  – Negative rheumatoid factor test
Differential Diagnosis
4. MPGN related to hepatitis C infection

• Pro:
  – Proliferative glomerulonephritis
  – Hepatitis C virus positive patient

• Contra:
  – Large glomerular capillary deposits and “hyalin thrombi” (although these can be focal and may be absent in the biopsy)
  – Distinctive substructure in the deposits
  – Undetectable hepatitis C viral load
Differential Diagnosis

5. PGNMIGD

• Pro:
  – Proliferative GN with IgG1 Kappa deposits

• Contra:
  – Presence of cryoglobulin
  – Paracrystalline substructure in the deposits
6. Monoclonal IGGDD (Randall type)

- **Pro:**
  - Monoclonal IgG1Kappa deposits

- **Contra:**
  - Absence of extraglomerular deposits
  - Absence of finely granular punctate deposits
  - Paracrystalline substructure in the deposits
Differential Diagnosis
7. Diffuse proliferative lupus nephritis

• Pro:
  – Hypercellular glomeruli with large “glassy” glomerular capillary deposits (“wire loop lesions”) and glomerular capillary hyalin thrombi
  – Endothelial tubuloreticular inclusions
  – Low C3 and C4

• Contra:
  – Everything else
## Characteristic Renal Biopsy, Laboratory and Clinical Findings in Cryoglobulinemic Glomerulonephritis

<table>
<thead>
<tr>
<th>Type of Cryoglobulin</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular hypercellularity</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Glomerular capillary hyalin thrombi, large deposits</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Vasculitis in the biopsy</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Distribution of deposits</td>
<td>Diffuse global</td>
<td>Can be focal segmental</td>
<td>Diffuse global</td>
</tr>
<tr>
<td>IgG in deposits</td>
<td>Monoclonal</td>
<td>+++ Polyclonal</td>
<td>++ to +++ Polyclonal</td>
</tr>
<tr>
<td>IgM in deposits</td>
<td>Monoclonal (there may be nonspecific entrapment in IgG monoclonal cases)</td>
<td>+++ (IgM kappa)</td>
<td>++ to +++ Polyclonal</td>
</tr>
<tr>
<td>Substructure in deposits</td>
<td>Paracrystalline/crystalline</td>
<td>Microtubular</td>
<td>Usually none</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>+/- (if IgM)</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Monoclonal spike in serum</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Low serum C3</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Low serum C4</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Hepatitis C virus</td>
<td>-</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Infection, acute/active inflammation, autoimmune disease, malignancy</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>B-cell lymphoproliferative disease</td>
<td>++</td>
<td>-</td>
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Hepatitis C Virus and Lymphoma

• In Hepatitis C + patients, there is a 3 to 5 fold increase of lymphoma relative to the “normal” population

• Most lymphomas are low grade (Marginal zone lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma)

• Relatively indolent course; in many patients anti-viral treatment is sufficient to induce remission
“Occult” Lymphoma

- Using high sensitivity flow cytometry, monoclonal B cells can be detected in 10% of adults >60 yrs of age.
- Monoclonal B cell populations can be detected in “reactive” lymphoid tissues with antigen-driven hyperplasia.
- Most of these patients have no “MGUS” and do not appear to progress to overt lymphoma.
- Can they have a “renal significance”? 
Summary/Conclusions

• The Correct diagnosis and classification of cryoglobulinemic GN in renal biopsies can be difficult.
• Not all biopsies with features of cryoglobulinemic GN from hepatitis C virus positive patients represent type II cryoglobulinemia-associated GN
• Hepatitis C virus positive patients have an increased risk of B cell lymphomas, which can be associated with monoclonal immunoglobulin deposits, including monoclonal cryoglobulins
• Early clonal B cell populations may be difficult to detect (“occult” lymphomas?)
• PCR based Ig heavy chain gene rearrangement study is a sensitive method to detect small monoclonal B cell populations in routine paraffin embedded tissue; we have now a low threshold requesting this study in kidney biopsies