WHAT IS A CRYOGLOBULIN & WHY SHOULD I CARE?

Morie Gertz
Mayo Clinic
72 y.o. Female
Mild anemia (Hb: 10.7g/dL)
Microscopic hematuria, RBC casts
Mild proteinuria (0.5gr/24 hour)
Elevated ESR
Normal creatinine
Further Workup

1. Serum protein electrophoresis
2. Urine protein electrophoresis
3. Renal biopsy
4. All the above
The patient underwent a renal biopsy which showed a membranoproliferative glomerulonephritis with immunofluorescence positive for IgM, kappa light chain, C3
Two glomeruli showing proliferative intracapillary lesions and intense immunocomplex deposits in capillary walls (short arrows) and subendothelial, giving the picture of pseudothrombi (long arrows) (H-E, x300).
Intense representation of the subendothelial deposits giving the picture of pseudothrombi (arrows) (H-E, x400).
Differential Diagnosis

- Systemic Lupus Erythematosus
- Cryoglobulinemia
- Idiopathic Gromenulonephritis
- Renal Amyloidosis
- Light Chain Deposition Disease
- Fanconi’s Syndrome
• Anti-DNA → negative
• Cryoglobulins → positive
• SPEP → small m-spike in beta-gamma region
• IF → IgMk
  ↓
  cryoglobulinemia
• hepatitis B, C → negative
• Rheumatoid Factor → positive
• Precipitation of blood proteins at temperatures lower than 37°C is referred to as cryoprecipitation

• Cryoglobulins are either immunoglobulins or a mixture of immunoglobulins and complement components that precipitate from both serum and plasma (if just plasma, then called cryofibrinogen)
Renal Pathological Findings

- **Light and immunofluorescence microscopy:** In Mixed CG, most common is membranoproliferative glomerulonephritis (60–80%), with endocapillary proliferation and subendothelial and/or intraluminal deposits of CGs, immunoglobulin, and/or complement proteins.

- **Type I CG generally produce noninflammatory glomerulopathies,** including thrombotic and hypocellular lesions, without evidence of vasculitis.
Clinical Presentation – Type II

- Cutaneous – erythematous macules that develop into purpuric papules on the lower extremities
  - Seen in 90–95% of patients
  - Usually leukocytoclastic vasculitis
Musculoskeletal: Arthralgias and myalgias are common in type Type II and III CGs (>70%). Most commonly affect metacarpophalangeals, proximal phalangeals, knees, and ankles.

Neuropathy: Affects 70–80% of pts with mixed CG (Type II & III). Thought to be 2/2 (unclear to me what 2/2 means) vasculitis.

Pulmonary: Generally affects Types II & III (40–50%). PFTs often reveal evidence of small airways disease and impairment of gas exchange; sx generally range from dyspnea to cough and pleurisy.
Next Step

- Start treatment
- Bone marrow biopsy
Bone Marrow Biopsy

- 70% infiltration by small lymphocytes, lymphoplasmacytoid cells, and plasma cells. The infiltration pattern is interstitial and in some places diffuse. There are mast cells seen (5%)
- Immunophenotype on lymphocytes: CD20+, CD79+, cIgM (k)+, CD5-, CD23-
- Immunophenotype on plasma cells: CD138+, IgM (k)+
Treatment Choice

1. interferon alpha
2. chlorambucil
3. chlorambucil + prednisone
4. nucleoside analogue (fludarabine, cladribine)
5. rituximab
6. combination treatment
History

- Precipitation on cooling of serum was reported by Wintrobe and Buell in 1933
- Term cryoglobulin coined by Lerner & Watson 1947
- Meltzer & Franklin 1966 cryo with arthralgia, purpura, neuropathy, nephropathy
Classification

- Type I: G, A or M common incidental findings in myeloma with cryocrits of 100%. Rarely relevant rather interesting lab phenomenon does not form immune complexes i.e. no vasculitis.

- Type III polyclonal uncertain whether this represents a true disorder.
Classification

- Type II (mixed) Monoclonal almost always IgM with polyclonal IgG thus by definition a RF generally high titer. Immune complex fixes compliment-note confusion with rheumatoid vasculitis
Monoclonal Gammopathies
Mayo Clinic

n=31,479

MGUS 61% (19,042)

Multiple myeloma 17% (5,439)

SMM 4% (1,178)

Lymphoproliferative 3% (951)

Amyloidosis (AL) 9% (2,815)

Solitary or extramedullary 2% (656)

Macro 2% (699)

Other 2% (699)
### Monoclonal Gammopathies

#### Mayo Clinic

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosclerotic (POEMS)</td>
<td>139</td>
</tr>
<tr>
<td>Plasma cell leukemia</td>
<td>75</td>
</tr>
<tr>
<td>γ heavy-chain disease</td>
<td>28</td>
</tr>
<tr>
<td>μ heavy-chain disease</td>
<td>2</td>
</tr>
<tr>
<td>Benign hypergammaglobulinemia purpura of Waldenström (BHPW)</td>
<td>31</td>
</tr>
<tr>
<td>Light chain deposition disease</td>
<td>63</td>
</tr>
<tr>
<td>Acquired Fanconi syndrome</td>
<td>36</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>227</td>
</tr>
<tr>
<td>Scleromyxedema</td>
<td>23</td>
</tr>
<tr>
<td>Bence Jones Proteinuria</td>
<td>29</td>
</tr>
<tr>
<td>Cold agglutinin disease</td>
<td>46</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>699</strong></td>
</tr>
</tbody>
</table>
## MACROGLOBULINEMIA Definitions

<table>
<thead>
<tr>
<th>Monoclonal Serum IgM</th>
<th>Marrow Infiltration</th>
<th>Sx. Due to IgM Protein</th>
<th>Sx due to Tumor Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM Symptomatic</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>WM Smoldering</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IgM related disorder</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MGUS</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Cryoglobulins

- Highest association with illness are Type II Cryoglobulins ("mixed"), Monoclonal IgM + Polyclonal IgG by definition Rheumatoid Factors
- Usually complement fixing immune complexes
- Targets Skin, Liver, Kidney
- High Prevalence of HCB & HCV
In hepatitis clinics cryo is common usually Asx no lymphoma
"Essential" No identifiable underlying disease process

"Secondary" Chronic liver disease (HCV) Chronic infection (HCV) Lymphoproliferative disorder Connective tissue disease

Symptomatic cryoglobulinemia
- Purpura
- Weakness
- Neurologic
- Renal complications

"?" represents unknown contributing factors

Serum cryoglobulins

No symptoms of cryoglobulinemia
### TABLE III. Symptoms by Cause of Type II Cryoglobulinemia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type II cryoglobulinemia without comorbidity (N = 10)</th>
<th>HCV (N = 40)</th>
<th>LPD (N = 16)</th>
<th>Rheumatologic disease (N = 8)</th>
<th>Allb (N = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>P</td>
<td>n</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Purpura</td>
<td>5 (50)</td>
<td></td>
<td>20 (50)</td>
<td>9 (56)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>4 (40)</td>
<td>0.037</td>
<td>3 (8)</td>
<td>0.041</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0</td>
<td></td>
<td>3 (8)</td>
<td>2 (13)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (30)</td>
<td></td>
<td>9 (23)</td>
<td>2 (13)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (10)</td>
<td></td>
<td>9 (23)</td>
<td>3 (19)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Cutaneous ulcer</td>
<td>1 (10)</td>
<td></td>
<td>2 (5)</td>
<td>0.10</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>1 (10)</td>
<td></td>
<td>1 (3)</td>
<td>0.032</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Digital infarct</td>
<td>1 (10)</td>
<td></td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal disease</td>
<td>2 (20)</td>
<td></td>
<td>10 (25)</td>
<td>7 (44)</td>
<td>2 (25)</td>
</tr>
</tbody>
</table>
TYPE II CRYOglobulinemia
in 66 Patients

- All Mayo patients 1994-2000
- M:F 45:55 Age 57
- Hepatitis C 58% Ten genotype 1a or 1b & Two were 2a or 2b.
- Of HCV + patients 21% also had HBV
- One Each of CMV & EBV infection
CRYOLOBULINEMIA

Presenting Symptoms

- Purpura: 52%
- Edema: 24%
- Neuropathy: 18%
- Fatigue: 18%
- Arthralgia: 15%
- Wt Loss: 12%
- Livedo R.: 8%
- Ulcer: 6%
- Infarction: 3%
Summary of Clinical Manifestations in 1,033 Patients with Essential Mixed Cryoglobulinemia

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpura</td>
<td>82%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>42%</td>
</tr>
<tr>
<td>Weakness</td>
<td>45%</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>42%</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>34%</td>
</tr>
<tr>
<td>Raynaud's phenomenon</td>
<td>22%</td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td>6%</td>
</tr>
</tbody>
</table>

CRYOGLOBULINEMIA
Clinical Associations

- Skin Ulceration more frequent in patients with underlying LPD
- Neuropathy & Raynauds more common in Autoimmune Patients
- Purpura alone does not require therapy
CRYOGLOBULINEMIA

Serum Protein Electrophoresis

- Normal
- Poly
- Hypo
- M-spike
- M-spike+poly
Type II (IgG-IgMκ) Cryoglobulin
Clinical Manifestations

- **Musculoskeletal:** Arthralgias and myalgias are common in type Type II and III CGs (>70%). Most commonly affect metacarpophalangeals, proximal phalangeals, knees, and ankles.

- **Neuropathy:** Affects 70–80% of pts with mixed CG (Type II & III). Thought to be 2/2 (unclear to me what 2/2 means) vasculitis.

- **Pulmonary:** Generally affects Types II & III (40–50%). PFTs often reveal evidence of small airways disease and impairment of gas exchange; sx generally range from dyspnea to cough and pleurisy.
Cryoglobulinemia

Associated Disorders

- Sjogrens 7, Scleroderma 1, 11
  Lymphoproliferative disorder at diagnosis & 5 more LPD’s at follow up
- Pathology MALT in 4
- Renal Disease seen in 35% MPGN & MesangioPGN
TYPE II CRYOGLOBULINEMIA
PATIENT UNDERLYING DISORDERS

- HCV
- LPD
- Autoimm
- "Essential"
Cryoglobulinemia

Laboratory Findings

- Mean cryocrit 7.6%
- All + Rheumatoid Factor
- Hypocomplementemia 80%
- SPEP patterns: Normal 46%, Polyclonal 10%, Hypoγ 10%, Discrete Band 34%
- κ:λ 88:12
Cryoglobulinemia

Therapy

• No Treatment Required 30%
• Of 38 HCV+, 17 α-IFN ± Ribavirin, 2 corticosteroids
• Of 28 HCV -, 20 corticosteroids
• Among 46 treated patients 27 (59%) had no response or disease progression.
• Only 8 of 66 died none due to cryog.
# Pre Rituximab Rx of Cryo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Renal disease</th>
<th>Cutaneous ulcer</th>
<th>Neuropathy</th>
<th>Dermatologic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>16/23</td>
<td>7/11</td>
<td>4/9</td>
<td>21/24</td>
</tr>
<tr>
<td>IFN</td>
<td>4/5</td>
<td>1/1</td>
<td>0/0</td>
<td>7/7</td>
</tr>
<tr>
<td>IFN + ribavirin</td>
<td>0/0</td>
<td>0/1</td>
<td>0/1</td>
<td>4/6</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>8/10</td>
<td>1/1</td>
<td>0/1</td>
<td>5/7</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2/4</td>
<td>1/1</td>
<td>1/2</td>
<td>2/2</td>
</tr>
<tr>
<td>Total</td>
<td>30/42</td>
<td>10/15</td>
<td>5/13</td>
<td>39/46</td>
</tr>
</tbody>
</table>

Note. IFN, interferon.

*Values are $\frac{\text{No. of patients who had a response}}{\text{No. of patients who received the treatment}}$.  

**TABLE V. Most Common Treatments and Number of Patients with Complete or Partial Improvement**

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Rituximab & Cryoglobulinemia

- 8 patients with previously treated symptomatic CG received 14 total courses of rituximab treatment (standard infusion, 375 mg/m² for 4 or 8 doses). Six patients had an LPD, and 4 of them had concomitant disorders (2 with hepatitis C and 2 with Sjögren syndrome).
Rituximab & Cryoglobulinemia

- Treatment indications included LPD, cutaneous ulcers, and renal failure. Clinical improvement was evaluated by improved cryocrit, total complement, C4, and rheumatoid factor. Six patients had some clinical improvement. Cutaneous manifestations were the most responsive.
Renal disease and lymphoma were more refractory. Laboratory values showed improvement after 7 of 12 available treatment courses. No adverse reactions were noted. Overall, rituximab appears to be a safe and effective therapy.
Survival of Mayo Cohort

Fig. 1. Kaplan–Meier survival curve for all study patients.

Fig. 2. Kaplan–Meier survival curve for patient age greater or less than 56.7 years old.
57 cases from two uncontrolled series of 20 and 15 patients, and two smaller series of 6 and 5 patients. (All others form single or two case reports)

- chronic active HCV infection (75.4%)
- essential mixed cryoglobulinemia (24.6%).

55 of 57 pts had prior treatments for HCV (n=37) or immunomodulating treatments (corticosteroids, immunosuppressive drugs, plasma exchanges)

The main indication for rituximab therapy were

- non-responsiveness to other previous treatments (n=50)
- intolerance to previous treatments (n=3)
- associated lymphoma (n=2)

Most patients (48 of 57) received four weekly consecutive infusions of 375 mg/m2 of rituximab
Rituximab Treatment for Cryoglobulinemic Vasculitis

- Mean duration of follow-up after rituximab was 9.7 months (0.3 to 24).
- A clinical response (partial + complete/total) was recorded in:
  - 32 out of 40 (80%) patients for skin involvement,
  - 27 out of 34 (79.4%) for arthralgia, 27 out of 29 (93.1%) for neuropathy,
  - 15 out of 18 (83.3%) for glomerulonephritis
- A relapse of vasculitis was noted in 39% (93% were HCV-infected) after a mean of 6.7 months after last rituximab infusion
- 57% of relapsed patients who had after a second course of rituximab had complete remission
- There was no significant difference in the efficacy of rituximab therapy when patients presented with HCV-induced or essential cryoglobulinemia vasculitis

RESPONSE OF CRYO VASCULITIS TO RITUXIMAB

A
B
C
D
CRYOGLOBULINEMIA
Therapy & Survival

- Only 21% died, Only predictor of survival Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Response Rate%</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
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<tr>
<td>20</td>
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<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
</tr>
<tr>
<td>80</td>
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</table>

Therapies:
- Interferon
- Steroids
- Cyclophos
- Rituximab
CRYOGLOBULINEMIA Therapy & Survival

Response Rate based on Primary Indication for Rx

- Kidney
- Ulcers
- Neuropathy
- Skin

%
Symptoms

- No
  - Observe
- Yes
  - Type I cryo
    - Chemotherapy
    - Consider PBSCT
  - Type II or III cryo
    - Secondary
      - Treat underlying cause
  - "Essential" mixed cryo
    - Mild Sx
      - Conservative symptomatic care
    - Moderate Sx
      - HCV+ Interferon
    - Severe Sx
      - HCV- Pred,CTX or IS
      - Plasmapheresis and/or high-dose methylprednisolone


• Ferri C. Mixed cryoglobulinemia. Orphanet J Rare Dis. 2008 Sep 16;3:25. Review