Cryoglobulinemia

Paul Monach, MD, PhD
Boston University
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What are Cryoglobulins?

• Complexes of blood proteins that fall out of solution in the cold
  – This is a laboratory finding that does not usually recapitulated what is going on in the body!
  – Types I, II, and III
• Chemically, they are large immune complexes
  – Antibodies bound each other and usually also to their target “antigens”
Type I Cryoglobulins

- 10% of cases
- Always associated with a cancerous or pre-cancerous disorder of antibody-producing B cells
  - Waldenstrom’s, multiple myeloma, MGUS
- Monoclonal antibodies alone associate with each other and fall out of solution
  - No target antigen is needed
- Amount of cryoglobulin is very high, often > 10%
- Clinical syndrome, caused more by physical blockage of small vessels than by vasculitis
  - Severe skin disease especially in cold-exposed areas
  - Nerves, joints, kidneys also commonly affected
Type II and Type III Cryoglobulins

• 90% of cases = “mixed cryoglobulinemia”
  – 60% type II (monoclonal “rheumatoid factor”)
  – 30% type III (polyclonal “rheumatoid factor”)
  – No importance of II vs. III clinically!

• Causes
  – **Hepatitis C virus (HCV)** in 80% of cases
  – Rheumatic disease in 6% (Sjogren’s > lupus, RA)
  – Lymphoma in 4%
  – Unknown in 10% = “essential mixed cryoglobulinemia”

• Clinical syndrome, more from **vasculitis** than from blockage of vessels
Cryoglobulinemia, Henoch-Schonlein Purpura, and Skin-limited Vasculitis
Mixed Cryoglobulinemia - Clinical

• **Highly variable in severity**
  – Classic syndrome is “only” purpura, joint pain, and fatigue

• Skin (most common)
  – Purpura, ulcers, gangrene of fingers/toes

• Joints (common)
  – Often without swelling; does not cause permanent damage

• Nerves (common)
  – Often debilitating

• Kidneys (relatively common)
  – Variable severity, can be bad enough to lead to dialysis

• Heart, Lungs, Brain, Intestines
  – All uncommon (< 10%), but extremely dangerous
Diagnosis

• Cornerstone is a positive cryoglobulin test
• However...
  – It’s easy to do the cryo test improperly
  – 40% of patients with hepatitis C will have cryos at a low level, but only 1% have cryo vasculitis
  – Rheumatoid factor and complement (C3, C4) tests are more accurate but don’t prove vasculitis either
• Biopsy to prove vasculitis, or the characteristic pattern of kidney damage (MPGN) is often needed
  – Often the clinical picture and positive cryo test (or HCV and RF and low C4) are good enough
Treatment

- Type I: chemotherapy appropriate for the underlying B cell disorder
- Types II/III = mixed cryo
  - HCV-positive
    - Anti-viral therapy
    - If disease is severe, also rituximab
    - Most severe disease, often plasma exchange first
    - Role / dosing of prednisone is controversial
  - HCV-negative
    - Probably rituximab is best, but no studies to prove that
    - Role / dosing of prednisone is controversial
Prognosis

• If HCV is eradicated, that is usually curative
• If non-HCV or unable to eradicate HCV, usually recurs but can be treated the same way
• If associated with a B cell malignancy, depends on how well that cancer can be treated
• Involvement of brain, heart, or GI tract is life-threatening but uncommon
  – Neuropathy – frequently disabling
  – Severe kidney involvement – can lead to dialysis
• In mixed cryo, infection is the main cause of death
  – Are patients with cryoglobulinemia at particularly high risk?
  – Are we using too much prednisone?
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