Paraprotein-mediated renal damage and related deposition diseases

Paul F Shanley MD Jan 2010

1) **Paraproteins:**
    a. Definition: Monoclonal immunoglobulins or portions of immunoglobulins produced by a neoplastic proliferation of antibody producing cells
    b. Methods of detection: Protein electrophoresis and Immunofixation
    c. Multiple myeloma as the prototype paraprotein disease
        i. Criteria for diagnosis of myeloma
        ii. Kidney in multiple myeloma
            1. Proteinuria (~90% of patients)
            2. Bence-Jones proteinuria (~50% of patients)
            3. Renal insufficiency (> 50% of patients)
            4. Autopsy findings
                a. Cast nephropathy (30-50%)
                b. Primary AL-amyloidosis (~10%)
                c. Light chain deposition disease (~5%)
    d. Patterns of renal deposition determine clinical presentation (bulleted/bolded disease entities associated with each pattern are the main topics of this presentation):
        i. Isolated light chain deposition in glomerular basement membranes causes proteinuria or nephrotic syndrome
            - **Kappa light chain nephropathy**
            - **Amyloid nephropathy**
        ii. Light chain accumulation in proximal tubular epithelial cells causes cellular dysfunction and activation of cytokine-producing pro-inflammatory phenotype
            - **Fanconi syndrome**
            - **Chronic interstitial nephritis**
        iii. Light chain deposition occluding tubular lumens causes acute renal failure
            - **Myeloma cast nephropathy**
        iv. Whole immunoglobulin deposition in glomeruli causes combined hematuric and proteinuric syndromes (nephritic/ nephrotic)
            - **Cryoglobulinemia**
            - **Immunotactoid glomerulopathy**
    e. "Paraprotein related diseases"
        i. Not all amyloid, immunotactoid or cryoglobulin deposits are composed of paraprotein. These broader topics will be elaborated.
        ii. Not all Fanconi syndrome or chronic interstitial nephritis cases are due to paraprotein accumulation. The causes of these patterns of injury are beyond the scope of this presentation.

2) **Specific types of paraproteins produce distinctive patterns of deposition.**
    a. Injecting human Bence-Jones proteins into mice reproduce the specific patterns of cast formation, basement membrane deposition or fibril formation that was present in the patients from who the proteins were harvested [NEJM 324(26): 1845, 1991]
    b. Molecular features of the paraprotein correlate with patterns of deposition
        i. Light chains causing cast nephropathy have propensity to bind Tamm Horsfall protein
        ii. Amyloid is mostly λ ($V_\lambda 6$); when κ usually limited to
        iii. Kappa light chain nephropathy usually Vκ1 or Vκ4
        iv. Fanconi syndrome almost invariably Vκ1 with specific amino acid substitution causing incomplete catabolism (protease resistance)

3) Immunotactoid (Fibrillary and Microtubular) glomerulopathies

Development of knowledge
1977 - Congo red-negative, "amyloid-like" **fibrillary** deposits with IgG and C3
1980 - Parallel **microtubular** arrays containing Ig and C3 ("immunotactoid")
1990s – Controversy over nomenclature

	AL-Amyloid	Fibrillary-type Immunotactoid	Microtubular-type Immunotactoid	Light chain nephropathy
Congo Red	Positive	Negative	Negative	Negative
Fibril diameter & configuration	10 nm Random	20 nm Random	> 30 nm Parallel arrays	Dense granules No fibrils
Fibril composition	Monoclonal Ig light chains (usually lambda)	Whole Ig, usually polyclonal with component of IgG_4	Whole Ig, often monoclonal	Monoclonal Ig light chains (usually Kappa)
Associated diseases	Plasma cell dyscrasia		Hematologic malignancy	Plasma cell dyscrasia
Systemic deposition	Yes	Rare reports		Yes

4) Cryoglobulinemia

Development of knowledge and Classification
1933 Cryoprecipitates in a patient with multiple myeloma
1947 Purpura with "cryoglobulins"
(immunoglobulins that precipitate in cooled serum and re-dissolve on heating)
1966 Cryoglobulinemia clinical syndrome: purpura, arthralgia, weakness and renal disease
Characterization of the cryoprecipitates and identification of rheumatoid factor activity
1974 Brouet Classification

	Components of cryoprecipitate	Associated conditions
Type I	Monoclonal immunoglobulin	Waldenstrom's macroglobulinemia or multiple myeloma
Type II	Monoclonal rheumatoid factor (usually IgM kappa) and polyclonal immunoglobulin	Hepatitis C virus infection
Type III	Polyclonal immunoglobulin with antiglobulin activity against polyclonal immunoglobulin of a different isotype	Various autoimmune and inflammatory disorders

1992 Role of Hepatitis C virus in type II ("essential mixed") cryoglobulinemia [NEJM 327: 1490]

Pathology associated with cryoglobulinemia:
Systemic immune complex small vessel vasculitis
MPGN with cryothrombi occluding arterioles and glomerular capillaries